The Journal of Allergy

VOL. 12 MARCH, 1941 NO. 3

Original Articles

EFFECT OF VITAMIN C DEFICIENCY UPON SMOOTH MUSCLE RESPONSIVENESS TO NONSPECIFIC STIMULATION

HAROLD J. FRIEDMAN, M.D.
CLEVELAND, OHIO

CEVITAMIC acid has been reported by some workers[13-15, 20] to have a protective effect in guinea pigs against anaphylactic shock. Other investigators, however,[2, 3-6, 8, 9, 11, 15, 16] were unable to demonstrate such a protective action. Walzer[1] in his recent review of the literature on vitamin C and anaphylaxis stated "In few aspects of the subject has there been so little uniformity of opinion. Frequently different investigators have arrived at diametrically opposite conclusions."

Recently, Cohen[2] in an excellently controlled study on the effect of vitamin C on the sensitivity of guinea pigs to neoarsphenamine, and on anaphylactic shock, pointed out several of the common errors in the techniques employed in some of the previously reported investigations. He maintained that there were three important requirements for a properly controlled diet in such experiments: (a) The diet must really be adequate in all respects except for vitamin C; (b) the animal must have a sufficient quantity of acceptable food to obviate interference with the experiments by starvation; (c) the ration of vitamin C or of cevitamic acid must be planned upon a sliding scale corresponding to the tooth protection ration demanded by the increasing weight of the young animal.

The effect of vitamin C on the isolated strip of smooth muscle, as demonstrated by the Dale technique, has been reported in only two studies. Raffel and Madison[3] were unable to demonstrate any variation from the normal, in the response of isolated smooth muscle in the Dale bath when actively sensitized guinea pigs, on a normal laboratory diet, received daily subcutaneous injections of from 5 to 10 mg. of ascorbic acid throughout the period of sensitization. The general

From the Allergy Division of the Jewish Hospital, Brooklyn, New York.

anaphylactic response of guinea pigs on this regime did not differ in any way from that observed in normal guinea pigs. These workers also showed that in passively sensitized animals the addition of from 10 to 200 mg. of the vitamin C to the Dale bath, from two to 120 minutes before testing, had no effect on the specific response of the isolated strip to the added antigen. Hurwitz and Nicholls[4] found that, in animals which were kept on a "not fundamentally basic" but "fairly complete" diet except for a deficiency in vitamin C and which were sensitized to horse serum after scurvy had developed, a complete absence of specific contraction of the isolated strip of smooth muscle was noted in five of seven animals tested. These workers also noticed a definite diminution in the response of the uterine strips of scorbutic guinea pigs to histamine, pituitary extract, and barium chloride.

There are many reports on the general anaphylactic response of scorbutic guinea pigs and of guinea pigs fed an excess of vitamin C. Giroud and his associates[7] were unable to observe any difference in the anaphylactic response of normal guinea pigs and of those given an excess of vitamin C parenterally. Schafer,[8] however, believed that there was a slight increase in hypersensitivity in such animals. Konstansoff[9] reported that four days of complete starvation of sensitized guinea pigs prevented anaphylactic shock. Lesne and Dreyfus[10] reported the same results on sensitive rabbits. Pierret and Crampton[11] stated that complete starvation for thirty-six hours was sufficient to produce protection. Zolog[12] was unable to confirm these results. Solomonica[13] reported the complete protection of guinea pigs from anaphylactic shock by daily subcutaneous injections of vitamin C for three weeks prior to the sensitizing injection. Lemke[14] maintained that anaphylaxis could be diminished by subcutaneous injections of vitamin C, but Hochwald[15] could not confirm his results.

Walzer[1] pointed out that in many of the above studies no safeguards were taken to insure adequate feeding of protein, fats, carbohydrates, minerals, and necessary vitamins. The rapid loss of weight, anemia, and weakness manifested by many of the animals in the investigations may have been responsible for the results which were attributed to a deficiency of vitamin C. Cohen[2] controlled all these factors in his experiments. He reported that adequate vitamin C intake did not decrease the average incidence of anaphylactic shock nor did the lack of vitamin C increase this average incidence. This is in accord with the findings of Van Niekerk,[16] who found no change in the anaphylactic response when ascorbic acid was administered with the sensitizing antigen. Hochwald,[15] in the same type of experiment, could find no evidence that the anaphylactic response was influenced by vitamin C. He did, however, find a 50 per cent reduction in fatal anaphylaxis when large doses of vitamin C were given shortly before a shocking dose of antigen.

In view of these widely divergent reports and because of the lack of adequate dietary control in most of the reported experiments, a thorough study of the problem under rigidly controlled conditions seemed advisable.

The anaphylactic response in guinea pigs is essentially dependent upon two basic factors, (1) the development of precipitin antibodies and (2) the presence of a smooth muscle shock tissue. The effect of vitamin C upon the first of these factors has already been thoroughly investigated. Jusatz[17, 18] and his co-workers demonstrated that animals which were given intravenous injections of 100 mg. of vitamin C simultaneously with, or shortly after, the intravenous sensitizing injections of antigen developed higher precipitin titers than animals sensitized in the normal manner. He also observed that the precipitin-producing ability of scorbutic animals was diminished. Madison and Manwaring[19] and Raffel and Madison[3] also demonstrated the favorable influence of vitamin C upon antibody production. The relationship of vitamin C deficiency to the second factor, namely, its effect upon the smooth muscle shock tissue has never been adequately studied. The investigation of this significant factor was the aim of the present study.

Before the specific anaphylactic reaction of scorbutic guinea pigs could be reliably studied by the Dale technique, it was necessary to establish what influence scurvy, per se, might have upon the contractility of the smooth muscle. This could best be determined by investigations with a nonspecific excitant that could be employed in measured high dilutions. Since histamine can cause contraction of the isolated smooth muscle in the Dale bath in very high dilutions, this seemed an excellent excitant for this purpose.

The first step in such an investigation was to determine the smallest amount, i.e., highest dilution of histamine which, when added to the Dale bath, would produce a definite contraction of the smooth muscle of normal guinea pigs. One could then determine the influence of vitamin C deficiency on the reactivity of smooth muscle by making similar studies on animals in which varying degrees of scurvy had been induced.

TECHNIQUE

Animals.—Healthy, virgin, 250 Gm. female guinea pigs were used throughout the experiment.

Diet.—In the investigations requiring the feeding of a diet devoid of all vitamin C, the Purina Rabbit Chow (complete ration) as suggested by Cohen[2] was adopted as best suited for this work. This diet is well balanced in carbohydrates, fat, and protein. Its mineral content is high, and it supplies ample amounts of vitamins A, B, E, and G. Vitamin D is present in small amounts. The vitamin C content is negligible.

When the intake of protective quantities of vitamin C was desired, a solution of crystalline vitamin C, freshly prepared each day, was fed by means of a tuberculin syringe in doses which Cohen[2] showed were sufficient to give adequate tooth protection (0.7 mg. per 100 Gm. of body weight). Sufficient quantities of vitamins A and D were supplied by weekly feedings of 1 ml. of Haliver oil. Throughout the remainder of this paper, this diet consisting of the Purina Rabbit Chow and Haliver oil will be referred to as the scorbutogenic diet. Control animals were fed the normal laboratory diet which consisted of carrots, cabbage, and Pratts Complete Rabbit Pellets.

Histamine.—The histamine dilutions used for stimulating muscle strips were prepared from stock ampules of 1:1000 histamine hydrochloride. Fresh ampules were prepared every fourteen to eighteen days. Dilutions of 1:100 billion, 1:10 billion, 1:1 billion, 1:100 million, 1:10 million, 1:1 million, 1:100 thousand, and 1:10 thousand were made daily from the stock ampules. Dale-Ringer solution was used as the diluent.

DALE TECHNIQUE

For the most part, intestinal strips were used instead of uterine horns because the study was carried on through the summer months when guinea pigs tend to be in heat. At such times the uterine horns are engorged, irritable, and unreliable for Dale studies. To obtain the intestinal strips the animal was first killed by a sudden blow at the base of the skull. Empty sections of the intestines were selected for excision. Six strips, each about 0.5 inch in length, were removed from the animal after the attached mesentery had been carefully cleared away, with a minimum of trauma. One strip was then suspended in the Dale bath which was kept at a constant temperature of 39° C., and at a constant volume of 75 ml. The remaining strips were saved in another bath kept at the same temperature. A new strip suspended in a fresh bath was used for testing with each dilution. The amount of the histamine dilution added to the bath was always 1 ml.

RESULTS OBTAINED WITH CONTROLS

Control animals were divided into two groups. The first group consisted of twenty animals which were fed the normal laboratory diet. The second group, comprising six animals, was fed the scorbutogenic diet supplemented by daily feedings of vitamin C in doses calculated to provide adequate tooth protection (0.7 mg. per 100 Gm. of body weight).[2]

In a preliminary study it was found that the intestinal strips of normal guinea pigs tested with a 1:1 trillion dilution of histamine failed to respond in every instance, whereas definite contractions were frequently obtained with the 1:100 billion dilution. Testing, therefore, in the pres-

ent studies, was always begun with the 1:100 billion dilution and continued on new strips with increasing concentrations until a contraction was obtained.

TABLE I

THE RESPONSE OF SMOOTH MUSCLE TO DILUTIONS OF HISTAMINE IN ANIMALS ON A NORMAL LABORATORY DIET

G. P. NO.	WEIGHT (GM.)	ORGAN TESTED	RESPONSES WITH HISTAMINE DILUTIONS OF							
			1:100 BILLION	1:10 BILLION	1:1 BILLION	1:100 MILLION	1:10 MILLION	1:1 MILLION	1:100 THOUSAND	1:10 THOUSAND
200	250	I	−	±	±					++
202	280	I	−	±	+			+		
203	265	I	−	++						
201	335	I	±	++						
304	195	U	++++							
305	250	U	++++							
306	185	I	+	+						
307	190	I	++++							
308	240	I	+		++	++++				
309	260	I	−		−	+	++			
310	250	I	−	+	+++					
311	240	I	−	++	++					
313	260	I	−	+++						
314	240	I	±	++						
315	250	I	++	+++						
316	250	I	+	++						
317	185	I	−	++	++					
319	200	U	−	++++						
320	225	I	−	++++						
324	245	U	−	±	++	++++				

No positive reactions were obtained with 1:1 trillion dilutions of histamine.

I, Intestinal strip; U, Uterine strip; −, No contraction; ±, Doubtful contraction; +, Weak positive contractions; ++, +++, ++++, Definite strong contractions.

TABLE II

RESPONSE OF SMOOTH MUSCLE TO HISTAMINE IN ANIMALS ON A SCORBUTOGENIC DIET SUPPLEMENTED WITH ADEQUATE AMOUNTS OF VITAMIN C

G. P. NO.	WEIGHT AT ONSET (GM.)	DAYS ON DIET	ORGAN TESTED	WEIGHT AT TESTING (GM.)	RESPONSES WITH HISTAMINE TO DILUTIONS OF					
					1:100 BILLION	1:10 BILLION	1:1 BILLION	1:100 MILLION	1:10 MILLION	1:1 MILLION
215	255	35	I	340	−	++				
218	250	14	I	335	−		++			
217	200	37	I	290	−	++	+++			
216	255	20	I	260	−	++				
226	250	22	I	270	++	+++				
227	240	18	I	265	−	+++				

I, Intestinal strip.

In the twenty control guinea pigs which were fed on the normal laboratory diet the intestinal strips reacted to the 1:100 billion dilution in seven instances and to the 1:10 billion dilution in nine animals; two required the 1:1 billion dilution (Table I). Only two strips needed stronger than 1:1 billion dilution to produce contractions.

In the second control group, consisting of six animals receiving the scorbutogenic diet plus vitamin C, one strip reacted to the 1:100 billion

dilution of histamine, four required the 1:10 billion dilution, and in one the 1:1 billion dilution was necessary before a contraction could be elicited (Table II). A comparison of results obtained in both groups of controls (Tables I and II) revealed that in animals on a normal laboratory diet and in those on a scorbutogenic diet supplemented by adequate daily feedings of vitamin C, intestinal strips responded equally well to high dilutions of histamine. These results were confirmed in later experiments (Tables V and VI).

RESULTS WITH ANIMALS ON SCORBUTOGENIC DIET

In the first series of animals in these experiments, the guinea pigs were placed on the scorbutogenic diet described above, consisting of the Purina Rabbit Chow diet which was supplemented by 1 ml. of Haliver oil, fed at weekly intervals. The animals gained weight until the tenth day, after which time a gradual loss in weight occurred. Early signs of scurvy such as ruffled fur and slight weakness were first noticed on the eighteenth day. After twenty-two days of this dietary regime, the animals were sacrificed and their intestinal strips were tested with the various dilutions of histamine. Occasionally, when the uterine horns appeared to be in a normal state, they were also tested as a check on the intestinal strip reactions. The results obtained on the animals in this series are listed in detail in Table III. In none of these guinea pigs did the intestinal strip respond definitely (++) to a dilution higher than 1:10 million. Thirteen of the seventeen animals in the group required dilutions of 1:1 million or stronger before a definite contraction could be elicited. Only one animal in the series (G. P. 57) gave a reaction with the 1:1 billion dilution, and this was a weak response (+). These results seemed to demonstrate that, when animals were kept on a scorbutogenic diet for at least twenty-two days, stronger concentrations of histamine were needed to elicit contractions of their smooth muscle than were found necessary in normal guinea pigs.

The animals in the above series had already developed definite signs of scurvy before testing was begun on the twenty-second day. In the next series of animals (series II) testing was started on the tenth day of the scorbutogenic diet. By this time the animals had begun to show some loss of weight but no other manifest signs of scurvy. The results obtained in the nine animals in this series are tabulated in Table IV. The strips of seven animals reacted only when exposed to the dilutions of 1:1 million, 1:100 thousand, and 1:10 thousand. Only two gave reactions with 1:10 million. It was evident, therefore, that the intestinal strips of animals which had been kept on the scorbutogenic diet for ten days reacted to practically the same dilutions of histamine as those animals kept on the diet from twenty-two to thirty-three days. They required dilutions one thousand times as strong as those needed to produce contractions in the strips of normal animals.

TABLE III

THE RESPONSE OF SMOOTH MUSCLE TO HISTAMINE IN ANIMALS ON A SCORBUTOGENIC DIET FOR FROM TWENTY-TWO TO THIRTY-THREE DAYS (SERIES I)

G. P. NO.	WEIGHT AT ONSET (GM.)	WEIGHT AT TESTING (GM.)	NO. DAYS ON DIET	STATE OF HEALTH	ORGAN TESTED	RESPONSES WITH HISTAMINE DILUTIONS OF							
						1:100 BILLION	1:10 BILLION	1:1 BILLION	1:100 MILLION	1:10 MILLION	1:1 MILLION	1:100 THOUSAND	1:10 THOUSAND
14	260	220	22	R	U				±	+	++		
159	250	185	22	S	U		−	±	−	−	−	+++	+++
11	480	360	24	R	I	−			−	−	+++		
152	330	200	25	S	U					−	+	++++	
12	360	240	25	R	U				−	−	+	++	
22	320	270	26	R	U		−		−	−	+++		
101	330	240	26	S	I			−	−	−	−		+++
57	285	185	27	S	U		−	+		+		+++	
16	300	280	27	R	U			−		−		++	
13	410	290	27	R	I		−		−	++			
59	280	190	29	V.S.	U			−		−		++++	
17	250	200	30	V.S.	U			−			−	+	
18	240	200	30	V.S.	U			−	−		−	−	++
51	310	190	30	V.S.	I		±			−		+++	
63	300	230	32	S	I			±	−	+++			
64	320	240	33	S	I		±		−	−		+++	+
19	260	215	33	V.S.	U			−	−	−		++	++

R, Ruffled fur; V. S., Very sick; S, Sick; I, Intestinal strip; U, Uterine strip.

TABLE IV

THE RESPONSE OF SMOOTH MUSCLE TO HISTAMINE IN ANIMALS ON A SCORBUTOGENIC DIET FROM TEN TO SIXTEEN DAYS (SERIES II)

G. P. NO.	WEIGHT AT ONSET (GM.)	CONDITIONS AT TIME OF TESTING				RESPONSES WITH HISTAMINE DILUTIONS OF							
		WEIGHT (GM.)	DAYS ON DIET	STATE OF HEALTH	ORGAN TESTED	1:100 BILLION	1:10 BILLION	1:1 BILLION	1:100 MILLION	1:10 MILLION	1:1 MILLION	1:100 THOUSAND	1:10 THOUSAND
615	265	280	10	H	I				−	+	++		
616	260	250	10	H	I		−	−	−	−		−	+
619	270	270	11	H	I			−	−	−	++++		
625	290	290	11	H	U		−	−	−	++++			
626	280	290	12	H	I			−		−	−	+++	
612	270	260	12	H	I			−	−	−	−	+	
606	270	260	13	H	I			−	−	−	+		
604	295	270	14	H	I			−	−	−	++		
603	290	280	16	H	I				−		−		++++

H, Healthy; I, Intestinal strip; U, Uterine strip.

TABLE V

RESPONSE OF SMOOTH MUSCLE TO HISTAMINE IN ANIMALS AT DIFFERENT STAGES OF SCORBUTOGENIC DIET (SERIES III)

G. P. NO.	WEIGHT AT ONSET (GM.)	CONDITIONS AT THE TIME OF TESTING				RESULTS OBTAINED WITH HISTAMINE IN DILUTIONS OF							
		WEIGHT (GM.)	DAYS ON DIET	STATE OF HEALTH	ORGAN TESTED	1:100 BILLION	1:10 BILLION	1:1 BILLION	1:100 MILLION	1:10 MILLION	1:1 MILLION	1:100 THOUSAND	1:10 THOUSAND
100	260		0	H	I	−	±	±					++
101	260		1	H	U	+++							
102	270	280	2	H	I	−	±	++++					
104	255	280	3	H	U	−		−	−	−	+++		++++
105	250	280	4	H	I			−	−	+	++		
106	225	255	5	H	I	−	−	−		−	+		++
107	280	300	7	H	I	−		−	++				
108	275	310	8	H	I	−		−	−	+	+++		
109	280	335	9	H	I	−		−	−	±	++		
110	280	335	11	H	I	−		−	−	±	+	++++	
111	250	300	13	H	I	−		−	−		±	++	
112	270	350	15	H	I	−		−	±		±	++	+++
113	265	300	16	H	I	−		−	−	+	+++		
114	290	310	18	H	I	−		−	−	±	++	++	
115	260	210	20	R	I	−	−		−		++	+++	
116	270	240	22	R	I		−	−	−	−	+++		
117	290	250	24	S	I		−	−	−	+	++		
118	250	200	26	S	I	−	++	++		++			

H, Healthy; S, Sick; R, Ruffled fur; U, Uterine strip; I, Intestinal strip.

It now seemed important to determine how long guinea pigs could be kept on a diet devoid of vitamin C before the change in smooth muscle response to histamine became apparent. Nineteen guinea pigs in series III were therefore placed on the scorbutogenic diet. After the first twenty-four hours of the diet and at intervals of one or two days thereafter, one of the animals was killed and the intestinal strips were tested with histamine dilutions.

The results obtained in series III are tabulated in Table V. Up to the third day the animals reacted when dilutions of 1:1 billion or higher were added to the bath, i.e., within the same dilution range in which normal animals responded. After the third day of the diet stronger dilutions were necessary to elicit contractions. Only one exception to this occurred in the nineteen animals tested (G. P. 118). These findings seem to suggest that the sudden change in the responsiveness of the intestinal strip to histamine which occurred after the fourth day of the scorbutogenic diet was due to the vitamin C deficiency. This impression was strengthened by titrations to determine the vitamin C content of the bloods of four guinea pigs which had been fed the scorbutogenic diet for four, five, ten, and eighteen days respectively. These studies showed a complete absence of vitamin C in each instance.

In order to rule out any unknown variables in the above experiments which might pertain to season, animal groups, diet, etc., another batch of animals (series IV) was divided into three groups. Three of the animals were kept on the normal laboratory diet. Six were placed on the scorbutogenic diet but in addition were given daily feedings of protective doses of vitamin C. The remainder of the animals were fed the scorbutogenic diet alone.

The results of these experiments are tabulated in Table VI. In the three animals which were fed the normal laboratory diet, testing was done on the tenth, fifteenth, and twenty-ninth day respectively. Definite contractions were obtained with dilutions of 1:1 billion and 1:10 billion. Similarly, in those animals which were fed on the scorbutogenic diet plus adequate amounts of vitamin C, positive reactions were also elicited with either 1:1 billion or 1:10 billion dilutions. In the group fed only the scorbutogenic diet the animals tested on the first and second days responded to dilutions of 1:100 billion or 1:10 billion. The animals tested on the third day also responded normally, giving positive reactions to 1:10 billion and 1:1 billion. However, in the remainder tested from the fifth to the twenty-ninth day, contractions could be elicited only when the dilutions of 1:1 million or 1:100 thousand were used. Hence it was again demonstrated that the intestinal strips of guinea pigs fed on the normal laboratory diet and of those fed on the scorbutogenic diet plus adequate amounts of vitamin C responded to the same dilution of histamine. Animals on the scorbutogenic diet for three days or less were likewise responsive to the same dilutions as the

TABLE VI

SUMMARY OF RESULTS OBTAINED WITH VARIOUS DILUTIONS OF HISTAMINE IN MEMBERS OF A SINGLE GROUP OF GUINEA PIGS ON DIFFERENT DIETARY REGIMES

G. P. NO.	WEIGHT AT ONSET (GM.)	DIET	WEIGHT (GM.)	DAYS ON DIET	STATE OF HEALTH	ORGAN TESTED	RESPONSES WITH HISTAMINE DILUTIONS OF							
							1:100 BILLION	1:10 BILLION	1:1 BILLION	1:100 MILLION	1:10 MILLION	1:1 MILLION	1:100 THOUSAND	1:10 THOUSAND
202	250	N	280	10	H	I	–	±	++					
203	255	N	265	15	H	I	–	++						
201	250	N	335	29	H	I	–	±						
218	250	S + C	335	14	H	I	–		++					
216	255	S + C	260	20	H	I	–	++						
215	255	S + C	340	35	H	I	–	++						
227	240	S + C	270	18	H	I	–	+++						
217	200	S + C	290	37	H	I	–	++	+++					
226	250	S + C	270	22	H	I	++	+++						
119	250	S	265	1	H	I	–	+++						
120	220	S	240	1	H	I	+	+++						
121	260	S	265	2	H	I	–	++	++++					
122	230	S	240	2	H	I	–	+	++++					
123	240	S	250	3	H	I	–	–	+					
126	250	S	260	3	H	I	–	++	++					
212	240	S	270	3	H	I	–	–	+++	+++				
208	240	S	250	5	H	I		–	–	–	±	–	±	++
222	255	S	290	8	H	I	–		±	–	–	±	++	
206	250	S	260	11	H	I		–		–		±	++	
207	230	S	245	12	H	I			–		–	++		++
220	240	S	180	13	H	I						–	++	+++
223	255	S	235	14	H	I			–		±	–	+++	
221	220	S	220	19	R	I			–	–	–			+++
210	250	S	180	21	R	I		–	–	–		±	++	
214	250	S	175	29	V.S.	I			–	–	–	–	++	
219	215	S	180	26	V.S.	I			–	–	++	++		

N, Normal diet; C, Adequate dosage of vitamin C; S, Scorbutogenic diet; H, Healthy; I, Intestinal strip; R, Ruffled fur; V.S., Very sick.

two control groups (Table VI. G. P. 119-123, 126, 212). Those animals which had been fed on the scorbutogenic diet for longer than three days, but which had not shown any clinical signs of scurvy, reacted in the same manner as those animals which had developed definite clinical scurvy at the time of testing.

DISCUSSION

When the dietary regime suggested by Cohen[2] was followed it was possible to produce mild or subclinical scurvy in guinea pigs. For ten days following the use of such a diet, no gross physical changes were apparent. Between the eleventh and fourteenth days, such early symptoms of scurvy as slight ruffling of the fur and loss of weight were noted. Definite scurvy became apparent after eighteen to twenty days of the scorbutogenic diet. Thus, the intestinal strips of animals with vitamin C deficiency of varying severity were made available for testing with dilutions of histamine.

TABLE VII

SUMMARY OF RESULTS OBTAINED WITH DILUTIONS OF HISTAMINE IN ANIMALS ON A SCORBUTOGENIC DIET FOR THREE DAYS OR LONGER

SERIES	DAYS ON DIET	NO. OF ANIMALS	POSITIVE RESULTS OBTAINED WITH HISTAMINE IN DILUTIONS OF							
			1:100 BILLION	1:10 BILLION	1:1 BILLION	1:100 MILLION	1:10 MILLION	1:1 MILLION	1:100 THOUSAND	1:10 THOUSAND
I	22-23	17	0	0	1	0	3	4	7	2
II	10-16	9	0	0	0	1	1	3	2	2
III	3-26	15	0	0	1	1	0	9	3	1
IV	5-26	10	0	0	0	0	1	1	6	2

The intestinal strips of normal animals (Table I) and of animals which had been fed the scorbutogenic diet for three days or less (Tables V and VI) responded to histamine in dilutions of 1:100 billion, 1:10 billion, or 1:1 billion. Likewise strips of animals fed the scorbutogenic diet plus adequate daily doses of vitamin C (Tables II and VI) also reacted to these high dilutions. The intestinal strips of animals which had been fed the scorbutogenic diet for longer than three days (Table VII) responded only after being stimulated with histamine dilutions one thousand times as strong as those required for the control groups. The intestinal strips of animals with advanced scurvy reacted to the same dilutions of histamine as the strips of those animals which had been fed on the scorbutogenic diet only four days (Table VI). Animals on the scorbutogenic diet which were also fed vitamin C in quantities sufficient to provide necessary tooth protection (Tables II and VI) reacted in the same manner and to the same dilutions of histamine as did normal animals.

The foregoing experiments indicate that in guinea pigs, a deficiency of vitamin C causes a definite loss of smooth muscle responsiveness to

nonspecific stimulation. Jusatz,[17, 18] Madison and Manwaring,[19] and Raffel and Madison[3] have demonstrated that vitamin C influences the antibody response to specific antigenic stimulation. Jusatz and his associates,[17, 18] demonstrated a lack of precipitin-producing power in scorbutic animals. Vitamin C deficiency therefore directly influences two of the basic factors of anaphylaxis: (1) smooth muscle contractility and (2) antibody production. Both of these factors are impaired as a result of a deficiency of vitamin C. A decrease or absence of anaphylactic response may therefore be expected to occur in animals on a diet lacking in vitamin C.

Konstansoff[9] and Pierret and Crampton[11] reported that three or four days of complete starvation prevented the occurrence of the anaphylactic reaction. Hurwitz and his associates[4-6] obtained no specific contraction of the isolated smooth muscle in five of seven scorbutic guinea pigs and a definite diminution in the response of the strips of these guinea pigs to stimulation with histamine. All of these observations are of interest in the light of the results obtained in the present investigations. The loss of the anaphylactic response after a starvation period of three or four days, closely parallels the loss of smooth muscle responsiveness to histamine after three days of a diet lacking in vitamin C.

The writer's experiments have thus far dealt with the effect of vitamin C deficiency upon the response of smooth muscle to stimulation of a nonspecific nature. It now remains to determine the effect of such a carefully controlled diet upon the specific anaphylactic response of smooth muscle in the guinea pig as demonstrated by the Dale technique. The results of these experiments will be the subject of another communication.

CONCLUSIONS

1. The absence of vitamin C from the diet of guinea pigs diminishes the responsiveness of the smooth muscle to stimulation with histamine. In the muscles of scorbutic animals the minimal stimulating dose of histamine was at least one thousand times as great as that needed for muscle preparations obtained from normal guinea pigs.

2. The change in the response of smooth muscle becomes apparent on the fourth day of a scorbutogenic diet. After this time there is little or no further change in the response of the smooth muscle to stimulation with histamine.

REFERENCES

1. Walzer, M.: A Critical Review of the Recent Literature on the Dust Atopen and on Vitamin C in Relation to Hypersensitiveness, J. ALLERGY **10**: 72, 1938.
2. Cohen, M. G.: Vitamin C Deficiency: Sensitivity to Neoarsphenamine and Anaphylactic Shock, J. ALLERGY **10**: 15, 1938.
3. Raffel, S., and Madison, R. R.: The Influence of Ascorbic Acid on Anaphylaxis in Guinea Pigs, J. Infect. Dis. **63**: 71, 1938.
4. Hurwitz, S. H., and Nicholls, E. G.: Effect of Vitamin C Deficiency on Uterine Smooth Muscle in Sensitized and Non-Sensitized Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **28**: 139, 1930.

5. Hurwitz, S. H., and Wessels, A. L.: Reaction of Bronchial Smooth Muscle in Sensitized Guinea Pigs on a Vitamin C Deficient Diet, Proc. Soc. Exper. Biol. & Med. **29**: 122, 1931.
6. Hurwitz, S. H., and Wessels, A. L.: Reaction of the Perfused Isolated Lung of Sensitized Guinea Pigs to Horse Serum, Proc. Soc. Exper. Biol. & Med. **29**: 120, 1931.
7. Giroud, A., Giroud, P., Ratsimamanga, R., and Rabinowicz, M.: Pouvoir anti-anaphylactique de l'acide ascorbique chez le cobaye; importance de l'alimentation et du taux de l'acide ascorbique sur la sensibilité de l'organisme, Compt. rend. Soc. de Biol. **123**: 1146, 1936.
8. Schäfer, W.: Der Einfluss verschiedenen Vitamingehaltes der Ernahrung auf den anaphylakitschen Shock der Meerschweinchen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**: 385, 1937.
9. Konstansoff, C.: Le rôle de l'inanition dans l'anaphylaxie, Compt. rend. Soc. de Biol. **72**: 263, 1912.
10. Lesne, E., and Dreyfus, L.: Influence de la diete sur l'anaphylaxie, Compt. rend. Soc. de Biol. **71**: 153, 1911.
11. Pierret, A., and Crampton, C. W.: De l'action empechante de jeune sur le choc anaphylactique chez les animaux prepares, Compt. rend. Soc. de Biol. **89**: 1282, 1923.
12. Zolog, M.: Action de l'absence de Vitamine C sur l'anaphylaxie, Compt. rend. Soc. de Biol. **91**: 215, 1924.
13. Solomonica, B.: Vitamin C and Anaphylactic Shock, J. Immunol. **31**: 209, 1936.
14. Lemke, H.: The Modification of Anaphylactic Shock of Guinea Pigs With Vitamin C, Monatschr. f. Kinderh. **67**: 244, 1936.
15. Hochwald, A., and Schwarz, H.: Versuche über die Antikörperbildung nach Zufuhr von Askorbinsäure, Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**: 227, 1937.
16. Van Niekerk, J.: Anaphylaxis and Vitamin C, J. ALLERGY **8**: 446, 1937.
17. Jusatz, H. J., Bersin, T., and Köster, H.: Das Verhalten von Ascorbinsäure und Glutathion beim immunisierten Tier, Klin. Wchnschr. **14**: 1419, 1935.
18. Jusatz, H. J.: Der Einfluss der Vitamine auf den Immunitatszustand des tierischen Organismus. II. Wasserlosliche Vitamine, Ztschr. f. Immunitätsforsch. u. exper. Therap. **88**: 483, 1936.
19. Madison, R. R., and Manwaring, W. H.: Ascorbic Acid Stimulation of Specific Antibody Production, Proc. Soc. Exper. Biol. & Med. **37**: 402, 1937.
20. Schäfer, W.: Gewährt Askorbinsäure einen Schutz gegenüber dem anaphylaktischen Schock des Meerschweinchens? Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**: 394, 1937.

THE USE OF THEOPHYLLINE WITH ETHYLENEDIAMINE (AMINOPHYLLIN) FOR THE CONTROL OF BRONCHIAL SPASM

A Pharmacologic Study

Richard H. Young, M.D., Evanston, Ill., and Robert P. Gilbert, A.B., Chicago, Ill.

THE efficacy of intravenously administered theophylline with ethylenediamine (aminophyllin) for the relief of attacks of bronchial spasm has received considerable recognition. Priority of publication is claimed by Efron.[1] The first detailed study is that of Herrmann and Aynesworth,[2] who reported the results of forty-one intravenous injections of aminophyllin given to sixteen patients presenting attacks of status asthmaticus. Of these forty-one injections, thirty-one afforded prompt, complete, and persistent relief, and also, in practically all patients who had become adrenalin-fast, theophylline-ethylenediamine seemed to restore the sensitiveness to adrenalin. In a recent report, Efron and Everett[3] claim that fully two-thirds of "epinephrine-fast" cases of bronchial asthma are relieved by the use of aminophyllin intravenously. Numerous confirmatory reports in the form of isolated case reports have also been published.[4]

The drug is given intravenously, and the recommended dosage is 0.24 to 0.48 Gm. (3½ gr. to 7½ gr.) given in 10 c.c. of saline or glucose solution. Unfortunately there are occasional reactions, characterized by:[3] (1) severe pain if the solution is injected outside of the vein; (2) initial hyperpnea; (3) feeling of warmth, especially in the face; (4) burning sensation in the eyes; (5) metallic taste; (6) occasional nausea and vomiting. Possibilities of reactions may be avoided if the injection is given carefully and slowly. There are no reports of death resulting from the injection of theophylline-ethylenediamine intravenously.

We were interested only in the pharmacologic action of theophylline-ethylenediamine. Herrmann and Aynesworth,[2] and Efron and Everett[3] state that the mechanism of the action of the drug is not clear and that "the effects of xanthines on the cerebral vessels and on the bronchial musculature have not been experimentally established." However, there are two important studies on the pharmacology of the xanthine drugs which have a bearing on the mechanism of their action in the relief of bronchial spasm. Macht and Gin-Ching Ting,[5] in an experimental study on the action of antispasmodic drugs on the bronchi, using bronchial strips as a method of assay, found that all xanthine derivatives showed some bronchial dilator effect, caffeine being the

From the Department of Medicine, Northwestern University Medical School.
Aminophyllin used was furnished by G. D. Searle and Co.

weakest, and hypoxanthine, guanine, and adenine being most efficient. Theophylline-ethylenediamine (aminophyllin) was not assayed. Greene, Paul, and Feller,[6] studying the action of theophylline-ethylenediamine on intrathecal and venous pressures in cardiac failure and on bronchial obstruction in cardiac failure and in bronchial asthma, felt that the favorable influence on the dyspnea in the above conditions is related to a decline in the intrathecal and venous pressures. Our feeling was that, if a direct bronchodilating effect of theophylline-ethylenediamine could be shown, this would give the most adequate explanation of the effectiveness of this drug in relief of bronchial spasm.

PART I

EFFECT OF AMINOPHYLLIN ON ISOLATED BRONCHIOLES

Recently Sollmann and A. J. Gilbert[7] have developed an excellent method of demonstrating bronchial and bronchiolar reactions; this obviates the disadvantages of the bronchial strip method where one is limited to large bronchi and the perfusion method where bronchial edema and inability to localize exactly the site of reaction are encountered. Sollmann and A. J. Gilbert injected a warm 10 per cent gelatin in Ringer's solution into the trachea of the excised lungs of a rabbit, inflated them to approximately normal size, then tied off the trachea, and placed the lungs in ice-cold Ringer's solution in an icebox for one hour. Thin sections of lung tissue were then cut freehand with a sharp razor. The sections were placed in a shallow dish containing aerated Ringer's solution at room temperature. Each section was then pinned on a ring of cork cemented to the bottom of a Petri dish containing 50 c.c. of Ringer's solution. The Petri dish was then placed in the warm stage of a microscope, and the solution was heated to 37° C. Thirty minutes were allowed for recovery from trauma. Direct observation of bronchi or bronchioles could then be made through the microscope (best magnification, ×40 to ×100). Changes in the outline of the bronchioles were recorded by means of camera lucida drawings or motion picture filming. The only alteration in this procedure, which we found most satisfactory, was the use of a specially devised stage warmer (Fig. 1).

Addition of from 30 to 50 mg. of aminophyllin to the immersing fluid (aminophyllin 1:1,000) had little apparent effect on the relaxed bronchiole. However, aminophyllin had a definite protective action against the constrictor action of histamine. The routine procedure was as follows: (1) The reactivity of the bronchiole section was determined by the addition of 1 mg. of histamine hydrochloride (1:50,000) to the immersing fluid, and the degree of constriction was recorded by camera lucida drawings. (2) The same bronchiole section was washed three times with Ringer's solution, and a ten-minute rest period was given. (3) Aminophyllin (30 to 50 mg.) was added to the immersing fluid

(aminophyllin concentration, 1:1,000), and the degree of constriction of the bronchioles caused by the same quantity of histamine hydrochloride was recorded. (4) The section was rewashed, and histamine hydrochloride was added alone, as in the first step. The results as recorded by camera lucida studies are given in Table I. Cinematographic studies of a typical reaction were made, and illustrations from this film are shown in Fig. 2. In three of four trials, aminophyllin was found to hasten the relaxation time of bronchiolar sections constricted by histamine.

Fig. 1.—Petri dish warmer. Tissue is pinned to a cork ring cemented to the center of the Petri dish. Solution in the Petri dish is kept at 37° C. by running warm water (56° C.) through the hollow copper jacket.

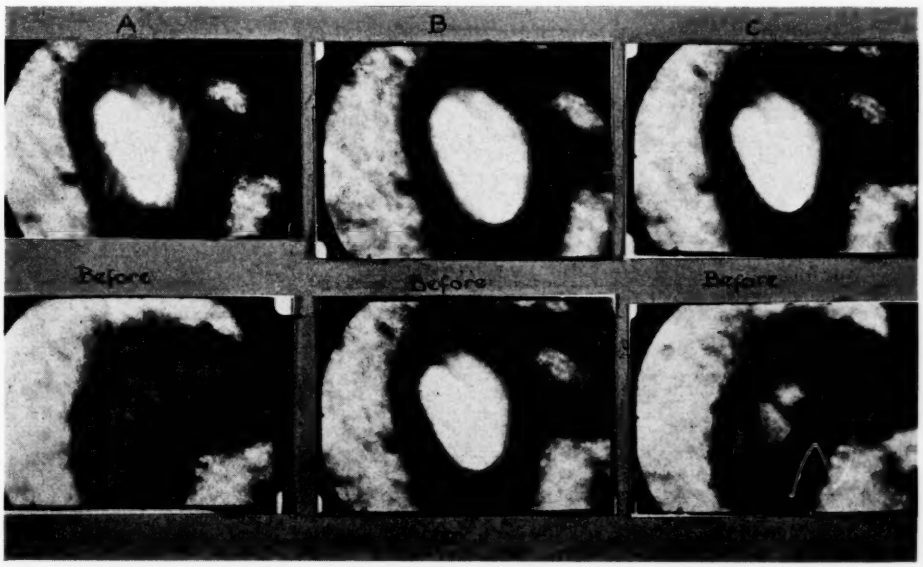

Fig. 2.—Bronchiolar reactions. *A*, Before and after addition of histamine 1:50,000 concentration. *B*, Same preparation after washing with Ringer's solution and an addition of aminophyllin 1:1,000 concentration followed immediately by histamine 1:50,000 concentration. *C*, Same preparation washed with Ringer's solution followed by an addition of histamine 1:50,000 concentration.

With the sodium salt of theophylline (concentration 1:2,000) and with theophylline alkaloid (concentration 1:5,000), no similar effect could be obtained. In view of this, ethylenediamine was tried, with completely negative results. The possibility that the marked alkalinity of the aminophyllin solution (pH 8.5) might be a factor in itself was

checked. When buffers and sodium hydroxide were used to raise the pH of the immersing solution to that of aminophyllin, no protective effect was seen.

TABLE I

PROTECTION OF AMINOPHYLLIN AGAINST THE CONSTRICTOR EFFECT OF HISTAMINE

BRONCHIOLE	INITIAL DEGREE OF CONSTRICTION TO HISTAMINE 1:50,000 (%)	DEGREE OF CONSTRICTION TO HISTAMINE 1:50,000 WHEN PRECEDED BY ADDITION OF AMINOPHYLLIN 1:1,000 (%)	RECHECK OF DEGREE OF CONSTRICTION TO HISTAMINE 1:50,000 (%)	PROTECTION AFFORDED BY AMINOPHYLLIN (%)
1	Not assayed	None	40	100
2	Not assayed	None	60	100
3	Not assayed	1-20	60	40
4	Not assayed	40	60	20
5	Not assayed	40	80	40
6	Not assayed	20	80	60
7	Not assayed	None	80	100
8	100	None	40	100
9	100	40	100	60
10	80	40	60	40
11	60	40	40	None
12	60	60	60	None
13	80	20	80	80
14	80	None	40	80
15	60	None	60	100
16	40	40	20	None
17	80	None	80	100
18	60	None	80	100

These results are based on camera lucida studies (percentages approximated). Negative results were obtained with sodium salt of theophylline, theophylline alkaloid, ethylenediamine alone, and buffer solution of the same alkaline pH of aminophyllin.

PART II

EFFECT OF AMINOPHYLLIN IN THE INTACT ANIMAL

An attempt was made to see whether aminophyllin would prevent bronchial spasm induced by histamine in the living animal. The minimal lethal dose of histamine given intravenously to guinea pigs is estimated as 0.1 to 0.3 mg. per kilogram of body weight.[8] All intravenous injections were made on the exposed jugular vein, and no anesthetic was used.

Of ten control guinea pigs, six received 0.4 mg. of histamine per kilogram; three, 0.29 to 0.3 mg. per kilogram; and one, 0.6 mg. per kilogram. Eight animals died in from two to five minutes, and two survived. Of the two surviving, one animal received only 0.29 mg. per kilogram; the other had been given histamine injections in a previous experiment, so there was some question of histamine desensitization in this case. Twenty-three guinea pigs were injected intravenously with theophylline-ethylenediamine in doses of 30 to 60 mg. per kilogram of body weight. Eighteen of these animals received 30 mg. per kilogram. Histamine hydrochloride was then injected intravenously in doses of

0.4 to 0.8 mg. per kilogram. Sixteen animals received 0.4 mg. per kilogram. Of the twenty-three animals, thirteen survived and ten died. Thus, there was a mortality of 80 per cent in the control group and of 56 per cent in the treated group. Table II gives the results of these experiments and a protocol of the autopsies.

TABLE II

PROTECTIVE EFFECT OF AMINOPHYLLIN IN THE INTACT ANIMAL

EXPERIMENT	NO. OF GUINEA PIGS	DOSAGE OF AMINOPHYLLIN INTRAVENOUSLY	DOSAGE OF HISTAMINE INTRAVENOUSLY	RESULTS
I. Histamine controls	10	0	0.29 to 0.6 mg. per kilogram (6 pigs were given 0.4 mg. per kilogram)	8 died within 2 to 5 min. 2 survived
II. Aminophyllin injection just prior to histamine treatment	23	30 to 60 mg. per kilogram (18 pigs were given 30 mg. per kilogram)	0.4 to 0.8 mg. per kilogram (16 pigs were given 0.4 mg. per kilogram)	13 survived 10 died

Experiment I.—Autopsy on dead pigs showed typical pulmonary inflation. Both surviving animals had severe respiratory symptoms. One was given 0.29 mg. of histamine; the other had had injections of histamine on previous occasions so there was question of desensitization in this case.

Experiment II.—Ten died; No. 2 lived 60 minutes; No. 3 lived 25 minutes and then died during the second attempt to inject aminophyllin. Histamine 0.8 mg. No. 5 received an incomplete injection of aminophyllin; Nos. 13 and 17 were given doses of histamine (0.6 mg. per kilogram). No. 14 died for no known reason. No. 18 had red hepatization of complete lobe of lung; No. 50 had abscess of the salivary gland. No. 31 had snuffles; the cardiac lobe of the lung was consolidated. One pig died twenty-four hours later; the cause of death was unknown.

Since the histamine-induced bronchial spasm is similar to the bronchial spasm occurring in anaphylaxis in guinea pigs, observations were made on the possible protective effect of aminophyllin against anaphylaxis. Forty-six guinea pigs were passively sensitized to horse serum. Of twenty-four untreated control animals, twenty-three died following the intravenous injection of antigen; of twenty-one animals receiving prophylactic administration of 30 mg. of aminophyllin per kilogram just prior to the injection of antigen, fifteen died. Therefore, there was a mortality of 96 per cent in the control group and of 71 per cent in the treated group.

DISCUSSION

Theophylline-ethylenediamine (aminophyllin) appears to have a definite protective action against the bronchoconstrictor activity of histamine. It would seem that its beneficial effect in the relief of attacks of bronchial asthma is caused by its action directly on the bronchial musculature. Since the publication of our preliminary report,[9] A. J. Gilbert and Goldman[10] have published a report on the effect of aminophyllin on bronchioles and conclude that aminophyllin is an effective dilator of bronchiolar sections poisoned by histamine.

In a study of the action of theophylline-ethylenediamine in the relief of Cheyne-Stokes respiration, Marais and McMichael[11] claim that the effect of the drug is by direct stimulation of the medullary respiratory centers and that the activity of the drug is caused mainly by its ethylenediamine component. We have no observations to contradict a possible direct respiratory center effect, but the action of the drug on the isolated bronchial rings speaks for a very definite local effect. In our hands, ethylenediamine alone, both on the isolated bronchial rings and in the histamine shock experiments, showed no beneficial effects.

The protective activity of aminophyllin against bronchospasm induced by intravenously injected histamine was definitely greater than that shown against the bronchospasm induced by anaphylaxis. However, we feel that the results in the anaphylactic shock experiments are probably significant. That there is no protection against anaphylactic shock manifestations other than bronchospasm was indicated by completely negative results in dog experiments where anaphylaxis was produced by both histamine and sensitization. (Dogs do not manifest as severe bronchoconstriction as do guinea pigs, during anaphylactic or histamine shock.)

The current views on the role of histamine in the production of anaphylactic shock and allergy have been reviewed by Dragstedt.[12]

CONCLUSIONS

1. Theophylline-ethylenediamine (aminophyllin) exerts a protective action against the bronchial constrictor effect of histamine.

2. The bronchial constrictor phenomenon seen in guinea pigs during histamine shock and anaphylactic shock is inhibited if the production of the anaphylactic shock is immediately preceded by an injection of theophylline-ethylenediamine (aminophyllin).

3. The action of theophylline-ethylenediamine (aminophyllin) would appear to be directly on the bronchial musculature.

REFERENCES

1. Efron, B. G., in discussion on Tuft, Louis, and Brodsky, M. L.: The Influence of Various Drugs Upon Allergic Reactions, J. ALLERGY **7**: 238, 1936.
2. Herrmann, G., and Aynesworth, M. B.: Successful Treatment of Persistent Extreme Dyspnea Status Asthmaticus, J. Lab. & Clin. Med. **23**: 135, 1937.
3. Efron, B. G., and Everett, Peter: Theophylline-Ethylenediamine (Aminophyllin) in Bronchial Asthma, New Orleans M. & S. J. **92**: 77, 1939.
4a. Brown, G. T.: Aminophyllin in Asthma, J. ALLERGY **10**: 64, 1938.
b. Hajos, K.: Erfahrungen über Asthmatherapie, Wien. klin. Wchnschr. **49**: 737, 1936.
c. Conferences on Therapy: Use of Drugs in the Treatment of Allergic Conditions, J. A. M. A. **112**: 1335, 1939.
d. Hyman, C.: The Intravenous Use of Aminophyllin in Bronchial Asthma, M. Rec. **150**: 279, 1939.
e. International Correspondence Club Allergy **1**: 70, 84, 97, 1938.
5. Macht, D. I., and Gin-Ching Ting, G.: A Study of Antispasmodic Drugs on Bronchus, J. Pharmacol. & Exper. Therap. **18**: 373, 1921.
6. Greene, J. A., Paul, W. D., and Feller, A. E.: The Action of Theophylline With Ethylenediamine, J. A. M. A. **109**: 1712, 1937.
7. Sollmann, T., and Gilbert, A. J.: Microscopic Observations of Bronchiolar Reactions, J. Pharmacol. & Exper. Therap. **61**: 272, 1937.

8. Schmidt, S. W., and Staehelin, A.: Histaminempfindlichkeit und anaphylaktische Reaktionen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **60**: 222, 1929.
9. Young, Richard H., and Gilbert, Robert P.: Use of Aminophylline (Theophylline-Ethylenediamine) to Control Bronchial Spasm Induced by Histamine, J. A. M. A. **114**: 522, 1940.
10. Gilbert, A. J., and Goldman, F.: Effect of Aminophyllin, Histaminase, and Nicotinic Acid on Histamine-Poisoned Puppy Bronchioles, Proc. Soc. Exper. Biol. & Med. **44**: 458, 1940.
11. Marais, O. A. S., and McMichael, J.: Theophylline-Ethylenediamine in Cheyne-Stokes Respiration, Lancet **2**: 437, 1937.
12. Dragstedt, Carl A.: Anaphylaxis and Allergy, Ann. Int. Med. **13**: 248, 1939.

PRECIPITINS IN THE SERA OF PATIENTS WITH CLINICAL ALLERGY

Preliminary Report

Milton B. Cohen, M.D., and Ross R. Weller, M.D.
Cleveland, Ohio

PREVIOUS to the demonstration of reagins by Prausnitz and Küstner no antibody had been demonstrated with regularity in the sera of atopic man. While the precipitin which is readily demonstrable in most anaphylactic animals is rarely formed in atopic man, various observers have suggested that it may be present, but in concentrations below the level at which it can be detected by the usual precipitin methods. Northrup,[1] Shibley,[2] and Eagle[3] have shown that the phenomena of agglutination and precipitation are essentially the same, differing only in the size of the particles undergoing aggregation. This reaction consists of two phases—the specific coating of the antigen particles by immune globulin, and salt precipitation of the coated antigen particles. Precipitin reactions are much less sensitive than agglutination reactions since the former deal with aggregates of molecules requiring the clumping of millions of particles to be visible, whereas the aggregation of relatively few bacteria makes the clumps easily seen. The sensitivity of the precipitin reaction can be increased successfully by coating the antigen on some inert particles, thus increasing the size of the particles to be aggregated and, in effect, converting it into an agglutination reaction.

Loeb,[4] Zozaya,[5] and Cannon[6] have described the preparation of collodion particles on the surfaces of which antigen can be coated. With these coated particles, Cannon has been able to demonstrate the presence of precipitin to egg white in sera of egg-sensitive animals which were negative by the ordinary methods. Some sera gave good reactions in dilutions as high as 1:400, showing the delicacy of the method. His report at the Chicago meeting of the Midwest Conference on Allergy that four or seven egg-sensitive patients had precipitin in their sera led us to study with this technique, the precipitin content of the blood of atopic patients.

The sera of ten patients sensitive to grass pollen, ragweed pollen, or fish glue were tested against their specifically coated antigen particles, with the results shown in Table I.

From the Asthma, Hay Fever, and Allergy Foundation. The expense of this investigation is being borne in part by a grant from Parke, Davis & Co.

TABLE I

PRECIPITIN CONTENT IN THE SERA OF ATOPIC PERSONS

CASE	TYPE OF SENSITIVITY	SERUM DILUTION									ANTIGEN
		10	20	40	80	160	320	640	1280	C	
M. L.	Glue and fish; untreated	2+	3+	4+	3+	2+	2+	+	0	0	Glue
Ma.	Ragweed; untreated	0	0	0	0					0	Glue
		0	0	0	0	0	0	0	0	0	Ragweed
		0	0	0	0	0	0	0	0	0	Grass
Wrob.	Ragweed; untreated	0	0	0	0	0	0	0	0	0	Glue
		0	0	0	0	0	0	0	0	0	Ragweed
N.	Normal serum	0	0	0	0	0	0	0	0	0	Glue
		0	0	0	0	0	0	0	0	0	Ragweed
		0	0	0	0	0	0	0	0	0	Grass
St.	Ragweed; untreated	+	+	+	±	0	0	0	0	0	Ragweed
McM.	Ragweed; treated	±	±	+	+	±	0	0	0	0	Ragweed
Fa.	Ragweed; treated	+	+	+	2+	2+	+	0	0	0	Ragweed
Br.	Ragweed; treated	+	+	3+	4+	4+	2+	+	0	0	Ragweed
Weiss	Ragweed, grass; treated	4+	4+	4+	4+	3+	+	±	0	0	Ragweed
		4+	4+	4+	4+	3+	2+	+	0	0	Grass
Sch.	Ragweed; treated	2+	3+	4+	3+	2+	+	0	0	0	Ragweed
		0	0	0	0	0	0	0	0	0	Grass
San.	Ragweed, grass; treated	+	+	2+	+	±	0	0	0	0	Ragweed
		+	3+	4+	3+	±	+	0	0	0	Grass

It will be noted that the fish- and glue-sensitive patient had precipitins against glue in a serum dilution of 1:640, but that two out of three untreated patients sensitive to ragweed showed no precipitin against ragweed. The one untreated patient had precipitins only in dilutions up to 1:40. In cases treated with ragweed or grass pollen, or both, precipitins against these antigens could be demonstrated with regularity.

REFERENCES

1. Northrup, J. H.: The Stability of Bacterial Suspensions, J. Gen. Physiol. **4**: 629, 1921-1922.
2. Shibley, G. S.: Studies in Agglutination, J. Exper. Med. **39**: 245, 1934.
3. Eagle, H.: Specific Agglutination and Precipitation, J. Immunol. **18**: 393, 1930.
4. Loeb, J.: The Influence of Electrolytes on the Cataphoretic Change of Colloid Particles and the Stability of Their Suspensions, J. Gen. Physiol. **5**: 109, 1922-1923.
5. Zozaya, J.: Carbohydrates Adsorbed in Colloids as Antigens, J. Exper. Med. **55**: 325, 1932.
6. Cannon, Paul: Personal communication.

STUDY ON REAGIN CONTENT OF SPINAL FLUID

McKinley London, M.D.
Cleveland, Ohio

ACCORDING to Merritt and Fremont-Smith,[1] normal cerebrospinal fluid contains none of the antibodies normally present in the blood; nor do any of the antibodies acquired as a result of vaccination or immunization by disease enter the spinal fluid through the intact choroid plexus or meninges. Kolmer[2] likewise says that cerebrospinal fluid is free of normal or natural antibodies. However, there is evidence to show that even in the uninjured state the choroid apparatus is not entirely impermeable. According to Kolmer,[2] in typhoid fever and other infections accompanied by a large amount of agglutinins in the blood, agglutinins in a lesser quantity will be found in the cerebrospinal fluid. Nelis,[3] after injecting Paratyphoid B into the blood stream of rabbits, demonstrated antibodies in the spinal fluid in low titer, when high titer was found in the blood stream. Sohier and his coworkers[4] recovered tetanus antitoxin in the spinal fluid of human beings passively immunized with tetanus antitoxin. These investigators[5] also demonstrated antitoxin in the spinal fluid of human beings actively immunized with tetanus and diphtheria toxins. Becht and Greer[6] found traces of bacterial agglutinins in spinal fluid of immunized dogs. Hektoen and Carlson[7] injected dogs with goat blood and found traces of lysins and agglutinins at the height of immunization in the spinal fluid. This combined experience clearly demonstrates that the above mentioned antibodies may traverse the choroid barrier.

So far we have been dealing with antibodies which show a comparatively ready diffusibility. The atopic reagin, however, has a strong affinity for fixed tissue and evinces a refractoriness toward passage through an anatomic membrane. Coca and Grove[8] have shown that local passive sensitization of the skin endures for at least four weeks. Precipitins and antitoxins readily pass the placental barrier; yet Bell and Eriksson[9] were unable to find reagins in cord blood from atopic women showing high titers of reagins in their blood. Zohn[10] made a similar investigation in artificially sensitized women. He injected prepartum women with extract of *Ascaris lumbricoides* until reagins appeared in the blood. Cord blood failed to show Ascaris reagins. Spain and Newell[11] and Parlato[12] demonstrated reagins in blister fluid

From the Allergy Clinic, St. Luke's Hospital, Cleveland, Ohio.

of atopic persons. They were dealing with fluid obtained by a process of inflammation, and therefore the passage of reagins cannot be considered to have taken place through tissue in a normal state.

EXPERIMENTAL DATA

Six persons sensitive to ragweed and one sensitive to grasses were subjects of this investigation. All showed at least a two-plus scratch reaction to pollen extract. One-tenth cubic centimeter portions of various dilutions of their blood sera were injected into the skin of persons proved to be capable of accepting passive transfer. The same was done by using 0.1 c.c. portions of undiluted spinal fluid. The following day the prepared sites were injected with approximately 0.02 c.c. of the appropriate extract with a 0.01 mg. total N concentration. In each case passive transfer was accomplished on at least four persons. The highest dilution of blood serum giving a one-plus reaction was adopted as the final reading. The spinal fluid was not diluted. Table I shows our results.

TABLE I

CASE NO.	HIGHEST SERUM DILUTION GIVING A ONE-PLUS REACTION	UNDILUTED SPINAL FLUID
Ragweed 1	1:2,000	Negative
Grass 2	1:400	Negative
Ragweed 3	1:350	Negative
Ragweed 4	1:300	Negative
Ragweed 5	1:300	Negative
Ragweed 6	1:200	Negative
Ragweed 7	1:100	Negative

CONCLUSION

We were unable to demonstrate reagins in the spinal fluid of atopic individuals, even when these were present in comparatively high concentrations in the blood.

REFERENCES

1. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, 1937, W. B. Saunders Co., p. 68.
2. Kolmer, J. A.: Infection, Immunity, and Biologic Therapy, ed. 3, Philadelphia, 1923, W. B. Saunders Co., p. 258.
3. Nelis, P.: La production des agglutinines spécifiques dans le sang et dans le liquide céphalorachidien des lapins soumis à une inoculation intraveineuse de bacilles paratyphiques B, Compt. rend. Soc. de biol. **126:** 172, 1937.
4. Sohier, R., Jaulmes, C., and Buvat, J. F.: Passage de l'antitoxine tétanique à travers la barrière vasculo-méningée chez l'homme au cours de l'immunisation passive, Compt. rend. Soc. de biol. **128:** 1079, 1938.
5. Sohier, R., Jaulmes, C., and Buvat, J. F.: Passage des antitoxines tétanique et diphtérique à travers la barrière vasculo-méningée chez l'homme au cours de l'immunisation active, Compt. rend. Soc. de biol. **129:** 281, 1938.
6. Becht, F. C., and Greer, J. R.: A Study of the Concentration of the Antibodies in the Body Fluids of Normal and Immune Animals, J. Infect. Dis. **7:** 156, 1910.
7. Hektoen, L., and Carlson, A. J.: On the Distribution of Antibodies and Their Formation in the Blood, J. Infect. Dis. **7:** 332, 1910.

8. Coca, A. F., and Grove, E. F.: Studies in Hypersensitiveness. A Study of the Atopic Reagin, J. Immunol. **10**: 445, 1925.
9. Bell, S. D., and Eriksson, Z.: Studies in the Transmission of Sensitization From Mother to Child in Human Beings, J. Immunol. **20**: 447, 1931.
10. Zohn, B.: Placental Transmission of Hypersensitiveness to Ascaris Lumbricoides Actively Induced in the Pregnant Woman, Am. J. Dis. Child. **57**: 1067, 1939.
11. Spain, W. C., and Newell, John M.: On the Reagin Content of Blister Fluid, J. ALLERGY **5**: 331, 1934.
12. Parlato, S. J.: Use of Blister Fluid for Passive Transfer Skin Test, J. ALLERGY **7**: 573, 1936.

SPONTANEOUS ALLERGY (ATOPY) IN THE LOWER ANIMAL

Seasonal Hay Fever (Fall Type) in a Dog

F. W. Wittich, M.D.
Minneapolis, Minn.

Bray's[1] observations of cattle and Vaughan's[2] of dogs are suggestive of allergy in animals. Tuft[3] mentions that sneezing and wheezing in dogs may represent symptoms of allergy "which have occurred spontaneously and possibly as the result of hereditary influence," but states "although these findings are suggestive, no definite proof of the existence of spontaneously occurring allergic manifestations in the lower animal has as yet been obtained."

This is an illustrated report of a female dog that has manifested typical hay fever symptoms for the past six years. These symptoms invariably correspond to the clinical appearance and disappearance of typical fall type of hay fever of patients in Minnesota. Her symptoms disappear promptly when she is removed to a relatively pollen-free area and reappear when subjected to weed pollen exposure. The case history and some of the results of skin, nasal, ophthalmic, and passive transfer tests follow.

CASE REPORT

This dog, living in Minneapolis, is a healthy, highly intelligent, nervous, ten-year-old female fox terrier. When she was 4 years old, her owner noticed that coincident with the fall hay fever season she began to have sneezing, tearing with conjunctival injection, nasal blocking, and a watery discharge accompanied by numerous small circumscribed swellings the diameter of a pea about her face and body. The swellings itched intensely as manifested by frequent violent scratching which produced excoriations on her face and body.

At various times during these attacks her fond owner had her under the care of three reputable veterinarians. It was thought that the diet was probably responsible for her condition or that she had parasitic skin lesions. These were excluded. At no time was the dog on any "canned" food and her diet as prescribed was strictly followed.

During the hay fever season she was taken to Duluth, on the shore of Lake Superior, where there is a relatively low pollen count. She became free of symptoms almost immediately. However, when she was allowed to run loose in the suburban lots, she developed mild symptoms. When she was taken back to Minneapolis during the hay fever season, the symptoms invariably returned within twenty-four hours.

For three years her owner has asked me if something could not be done about his "Mitzie's" hay fever.

After noticing in a local daily newspaper, Aug. 12, 1939, a picture of this dog with the caption "She Has Canine Hay Fever," I commenced the observations noted. Since the ragweed hay fever season usually starts August 5 to 11 in Minnesota, the

Colored motion picture shown before the 18th Annual Meeting of the American Association for the Study of Allergy, New York City, June 10, 1940.

dog had already been taken to Duluth. There, preliminary ophthalmic tests and nasal tests, as well as scratch tests, were made with short and giant ragweed. Definite typical hay fever symptoms as well as hives were produced about the face and body. The dog relieved herself by going through typical movements of lying on her side with her long nose closely hugging the grass and pushing herself backwards, describing a large circle. Then she would roll over and repeat the movements on the other side. She obtained relief after being given a capsule of ⅜ grain of ephedrine sulphate, ¼ grains of phenobarbital, and a concentrated epinephrine spray. No more experiments were permitted until May 12, 1940, when a colored motion picture was taken showing the nasal introduction of short ragweed. This was followed by the typical response of all the symptoms previously mentioned and the characteristic movements she goes through to relieve herself during the ragweed season. On May 17, 1940, subsequent pictures were taken showing the results of intradermal testing with a 1:1,000 dilution of short ragweed, giant ragweed, pigweed, Russian thistle, and prairie sage. These pollens represented the most important pollen groups causing clinical hay fever in this region. Typical skin responses were as follows: Short ragweed, ++++; giant ragweed, ++++; pigweed, ++; Russian thistle, +++; and prairie sage, ++++. Short ragweed and prairie sage produced larger wheals with pseudopods.

Fig. 1.

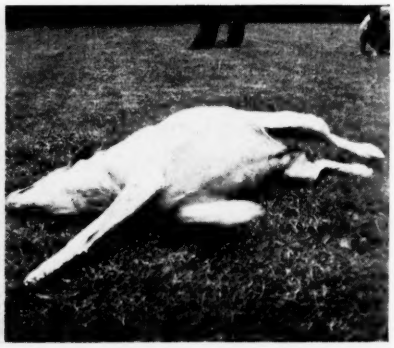

Fig. 2.

Fig. 1.—Characteristic movement of dog during the ragweed pollinating season and following ophthalmic test.

Fig. 2.—Characteristic movement of dog during the ragweed pollinating season and following nasal test.

Fifteen to eighteen minutes after the intradermal injections a systemic reaction resulted. She developed in order a marked edema of the left eye where an ophthalmic test had been made five days previously, nasal blockage, tearing, conjunctival injection, and urticaria which involved the face and trunk. She scratched her body, eyes, and nose sufficiently to cause bleeding. She vomited and appeared to be in shock. One cubic centimeter of 1:1,000 epinephrine was injected subcutaneously, and a concentrated epinephrine vaporizer was used. Four minutes later the dog became markedly relieved and in a few minutes was lively and acted normal although during the night there was a recurrence of symptoms which required ephedrine. One week later there were no demonstrable skin lesions, and she appeared to be normal.

No antibodies of the precipitin type were demonstrated. This has been the general experience with dogs in experimental anaphylaxis. Sherwood[4] claims to have shown that antibodies for antigens such as horse serum and crystallized egg albumen would stimulate the production of antibodies in dogs. These antibodies could be demonstrated by passively sensitizing normal dogs but could not be demonstrated by precipitin tests. Before hyposensitization treatments were commenced, passive

transfers to another dog of a different species as well as to a human being were successful. The dog herein described received a series of preseasonal hyposensitization treatments (tolerance dose 10,000 protein nitrogen units) of a combined extract of the weed pollens involved and passed through the height of the Minnesota weed pollinating season without any symptoms of hay fever and without skin lesions. Heretofore, she had rubbed the hair from her nose by the first week of August, and this was the first season she was not moved to a relatively pollen-free area.

Fig. 3.—Results of passive transfer tests to a dog of a different species. *1*, Pigweed; *2*, Russian thistle; *3*, short ragweed; *4*, prairie sage; *5*, giant ragweed; *6*, control.

COMMENT

Since observing this dog, I have been informed by veterinarians that they have seen symptoms of hay fever and asthma in dogs but did not recognize or suspect that they were allergic in origin and suggested distemper in some as an explanation. They have had owners of the dogs request that, if they could not relieve hay fever, the animals be put out of their misery. Two other dogs with similar symptoms have come to my attention. Fortunately they are of opposite sexes, and an endeavor to raise "atopic" pups will be tried.

It is interesting that laymen, ignorant of anaphylaxis and atopy, have apparently recognized this condition first.

A question of great interest that this case reopens is whether a sharp line can be drawn between anaphylaxis in the animal and allergy in the human. There are indications in the literature that such a separation cannot be made and that probably the underlying mechanism in man and animal are the same. Zinsser, Gay, Kolmer, Doerr, Wells, Ratner, Rackemann, and Vaughan consider experimental anaphylaxis and allergy as basically similar. This viewpoint is opposed by many of the contributors to clinical allergy, particularly those who subscribe to the concept of atopy which separates the allergy of man from that of animal. Zinsser[5] believes that the important differences between the two forms of hypersensitiveness are largely due to physiologic differences between animals and man and, to some extent, to the fact that dietetic and other habits of the human race are far more varied and stretch over much longer periods than those of animals. The acquisition of some forms of idiosyncrasy seems to require repeated exposure over more years than compose the lives of most laboratory animals.

Pirquet and Schick[6] in their monograph on serum sickness quote several hundred workers who report true serum sickness occurring spontaneously in animals, particularly in calves, after a primary injection of the anthrax antihorse serum. The time interval and symptoms are identical with those occurring in the nonallergic normal human being who receives antiserum.

Friedberger and Kamio,[7] after citing many examples of such reactions, draw the following conclusions: "At all events, these facts considered as a whole indicate that symptoms do appear after the first injection in animals, an occurrence which we must consider throughout as idiosyncrasy—allergy—in the sense in which Coca applied it. Because of the nature of the phenomenon, it was first noticed in our valuable house animals who were exposed to frequent contact with foreign sera and observed carefully afterward. The symptoms in animals often correspond so well with those of human beings, that Hutyra and Marek even speak of serum idiosyncrasy or diasthese and deny the appearance of true anaphylaxis in cattle, horses, and pigs as Coca does its appearance in humans."

Of great importance in the furtherance of this concept are the studies of Sewall[8] and Alexander,[9] who showed that guinea pigs could be sensitized by the inhalation of sprayed liquid antigens.

Ratner and his co-workers[10, 11] carried this work in guinea pigs to a point that more nearly resembles the spontaneous inhalant allergy in man. They used dry antigens in their native state, such as horse dander and castor bean, and through inhalation exposure demonstrated that these animals could develop symptoms that in all respects duplicated pollinosis and asthma. The eye symptoms and lung symptoms could be entirely brought about spontaneously through inhalation.

The work which bears directly on canine pollinosis is that of Ulrich,[12] who experimentally induced pollinosis in guinea pigs through insufflation of dry pollen.

It is hoped that many more observations will be forthcoming and a more complete picture of allergy in the domestic animal may finally tend to dispel the notion that allergy in man and animal should be separated. The fact that we were able to passively sensitize the human skin with dog's serum is of value in the furtherance of this concept.

CONCLUSIONS

1. Previous tests in season, and those done out of season, including direct skin, passive transfer, nasal, and ophthalmic, as well as successful hyposensitization on a dog having clinical hay fever symptoms would offer evidence that allergy can develop spontaneously in a lower animal.

2. If true, the terms allergy and atopy can be applied to hypersensitivities occurring naturally in any animal species including man, and the term anaphylaxis to that phenomenon which is artificially induced in man or animal.

3. The terms allergy, atopy, and anaphylaxis in their broadest meanings can therefore be used interchangeably to describe the hypersensitive state either in man or in the lower animal.

I am very grateful to Mr. R. N. Finch, owner of the dog, and to Dr. F. W. Gehrman, V.S., for their cooperation and assistance.

REFERENCES

1. Bray, Geo. W.: Recent Advances in Allergy, ed. 3, Philadelphia, 1937, P. Blakiston's Son & Co.
2. Vaughan, Warren T.: Practice of Allergy, St. Louis, 1939, The C. V. Mosby Co.
3. Tuft, Louis: Clinical Allergy, Philadelphia, 1937, W. B. Saunders Company.
4. Sherwood, Noble P.: Personal communication. Department of Bacteriology, University of Kansas.
5. Zinsser, H. T.: Resistance to Infectious Diseases, ed. 4, New York, 1931, The Macmillan Company.
6. Pirquet, C. F. Von, and Schick, B.: Die Serum Krankheit, Leipzig and Wien, 1905, Franz Deuticke.
7. Friedberger, E., and Kamio, T.: Can a Relation Be Proved Between Asthma and Experimental Anaphylaxis in Guinea Pigs? Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**: 379, 1923.
8. Sewall, H.: Experimental Asthma in the Guinea Pig, J. Lab. & Clin. Med. **2**: 874, 1917.
9. Alexander, H. L., Becke, W. G., and Holmes, J. A.: Reactions of Sensitized Guinea Pigs to Inhaled Antigens, J. Immunol. **11**: 175, 1926.
10. Ratner, Bret, Jackson, H. C., and Gruehl, H. L.: Ocular Manifestations in Anaphylaxis, Proc. Soc. Exper. Biol. & Med. **24**: 444, 1927.
11. Ratner, Bret: Experimental Asthma, Am. J. Dis. Child. **58**: 699, 1939.
12. Ulrich, H. L.: Experimental Pollinosis, J. Immunol. **3**: 453, 1918.

CUTANEOUS AND SYSTEMIC REACTIONS OBSERVED DURING ORAL POISON IVY THERAPY

BEDFORD SHELMIRE, M.D.
DALLAS, TEXAS

EXCLUDING shock therapy,[1] present data indicate that a fairly large amount of a plant oleoresin must be ingested to reduce appreciably skin sensitivity. Many common weeds, such as the *Baptisia, Crotalaria, Poinsettia, Lobelia, Delphinium,* and hemlock species, black nightshade, horsetail, jimson weed, locoweed, partridge pea, snow-on-the-mountain, and other plants are said to be poisonous when eaten. Extreme caution must be exercised when administering large amounts of a plant oleoresin, the toxicity of which has not been determined previously.

Approximately one of every four persons living in a district infested with poison ivy is clinically sensitive to the ivy vine or shrub. A high percentage of those affected would submit to prolonged oral therapy with the oleoresin of this plant if assured of a reduction in skin sensitivity and of the harmlessness of the procedure.

In order to study changes in skin sensitivity and to determine the toxic effects from prolonged ingestion of poison ivy oleoresin, varying amounts of this oil were administered orally to an ivy-sensitive, young adult female, a child's nurse employed in my home.

According to her history, the patient had suffered widespread attacks of ivy dermatitis on repeated occasions each summer since childhood. While in my employ, she developed three separate attacks of severe, generalized, vesicular dermatitis venenata. In each instance the source of the eruption was manual contact with the steering wheel of the family automobile which had been contaminated purposely with ivy oleoresin by gently rubbing the wheel with an ivy leaf.

After gathering poison ivy leaves, my hands were thoroughly washed with soap and water. The washing procedure was repeated at hourly intervals for six hours. At the end of this period, my hands were rubbed over the nurse's arms and forearms. After eighteen hours a typical ivy dermatitis developed at the contact sites.[2]

Uncovered patch tests on the forearms with serial dilutions of ivy leaf oleoresin in acetone in multiples of 10 gave vesicular responses to all dilutions from 1:10 to 1:1,000,000. Frankly positive patch reactions

Read before the Annual Meeting of the American Association for the Study of Allergy, New York, N. Y., June 10, 1940.

From the Department of Dermatology and Syphilology, Baylor University, Dallas, Texas.

were evoked on the back with dilutions up to 1:100,000, but not higher. Uncovered acetone dilutions of the oleoresin are much less antigenic than covered tests. Covered twenty-four-hour patch tests with the 1:100, 1:200, 1:500, 1:1,000, 1:5,000, and the 1:10,000 dilutions of ivy oleoresin in corn oil applied to the upper arms caused frankly vesicular reactions. The 1:20,000 dilution evoked doubtful reactions. Although covered and allowed to remain in direct contact with the skin for twenty-four hours, oil dilutions of ivy oleoresin are far less antigenic than acetone or ether diluted extracts of equal strength. Ether dilutions of the oil are slightly less antigenic than acetone extracts.

Patch tests were repeated for several months previous to the institution of oral therapy. These were applied principally to the supersensitive forearms, the most intense reactions always being elicited on the left arm. This woman was so markedly sensitive to poison ivy that 2 sq. cm. of skin of the left forearm were excised by Dr. J. H. Black and me, ground with sand and saline, passed through a Seitz filter, and injected into skin of the forearms of nonsensitive persons in passive transfer experiments. Patch tests with potent ivy extracts over the injected sites failed to demonstrate fixed antibodies in the nurse's excised skin.

Since the ingestion of the prescribed dosage could actually be observed and the skin and cutaneous reactions recorded daily in my home, this extremely sensitive volunteer was chosen for attempted desensitization to ivy.

Ivy Oleoresin Employed.—The antigenic potencies of oleoresins extracted from ivy leaves at different periods of plant growth often vary by several hundred per cent. The most antigenic oils are obtained from mature leaves gathered during the period ranging from the flowering stage of the plant until full maturity of the drupes (late spring and summer). The very young and the very old leaves yield oils of the lowest antigenic index. The oleoresins of young, immature leaves apparently do not contain as much of the dermatitis-producing fraction as the oleoresins of mature leaves. The large amounts of gums, waxes, and waste products of the very old leaves probably act as diluents, thereby rendering their oleoresins less antigenic. Bark of the branches and stems shows a similar seasonal antigenic variation. The ivy leaf oleoresins used in this experiment were extracted with ether from batches of dried leaves of *Rhus radicans* collected at various intervals during the late spring and summer months.

The antigenic potencies of oleoresins extracted from roots collected at different periods of plant growth showed no appreciable variations, but were found more potent than leaf oleoresins.[3] The root oils used in this experiment were extracted with ether from roots of *Rhus quercifolia* grubbed during January and April. The *R. radicans* from which

the leaf oils were extracted and the *R. quercifolia*, which furnished the root oleoresins, were found growing a few feet apart on a limestone hillside.

Some botanists still contend that slight differences exist between the various so-called species of the trifoliate, white-fruited forms of the *Rhus* family scientifically known as *R. radicans (R. toxicodendron), R. quercifolia, R. microcarpa, R. rydbergii, R. diversiloba*, etc., and commonly known as poison ivy or poison oak. They base their contentions on whether the plant grows erect or is a climbing vine and on variances in the texture, pubescence, and degree of lobing of the leaflets. Since all these variations can be observed in the same species under different climatic, soil, and other field conditions, conservative toxonomists now agree that the many species of poison ivy (poison oak) are identical. I have patch tested sensitive persons with acetone-diluted oleoresins extracted from mature leaves of many so-called species of poison ivy collected in different sections of the United States and have found the antigenic potencies of the various specimens to be identical. Soil and other field conditions apparently did not alter the potency of the many oleoresins tested.

Dilution of Oleoresin in Corn Oil.—Solvent-free leaf and root oleoresins were diluted with corn oil for oral treatment. Dilutions were made by volume and not by weight. The dropper employed throughout this experiment was of the ordinary bulb type fitted in a 1-oz. dropper bottle. This dropper delivered 27 drops of the ivy oleoresin-corn oil mixture per cubic centimeter at room temperature. The average of twenty bulb droppers purchased in the open market was 30 drops per cubic centimeter. Two drops of the ivy-corn oil dilution, therefore, equal approximately one minim. When administering large oral dosage, amounts were tabulated in capsules of 15 drops. The number one gelatin capsule, which was used, holds an average of 15 drops of this mixture. In computing the total amount of the ivy dilution ingested, 810 drops were considered to equal 1 oz. (27×30).

Absorption of Ingested Oleoresin.—At ten-day intervals from 5 to 20 c.c. of the 1:100 ivy oleoresin in corn oil were ingested by a volunteer who was nonsensitive to ivy or it was injected into multiple areas of his deltoid and gluteal muscles. Following administration of the oleoresin, the feces were collected for three days and the urine for five days. Concentrated ether extracts of the feces after either method of administration of the oil gave patch reactions of approximately equal intensity on ivy-sensitive persons. Control tests were negative. Paradoxical as it seems, extracts of urine collected after ingestion of the oleoresin routinely produced patch reactions of slightly greater intensity than extracts of urine collected after intramuscular injection of the oil. Control tests were again negative. Another contradictory finding was the

demonstration of large amounts of the oleoresin in the feces after the intramuscular injections of the excitant. Since the amount of ivy oil absorbed from the alimentary canal after ingestion of the oleoresin equaled that absorbed following its intramuscular injection, the oral route of administration of the excitant was chosen in the attempted desensitization of this ivy-sensitive nurse.

ORAL THERAPY

June 1 to September 13, 1939. Period of Fractional Dosage With Leaf Oleoresin.—On June 1 the nurse ingested one drop of a 1:200 dilution of ivy oleoresin in corn oil as an initial dose. The dosage was increased one drop each day until a maximum of 15 drops were ingested. This daily dosage was continued until 0.5 oz. of this dilution had been consumed. The concentration of the oleoresin was then increased to 1:100 and the initial dose was 10 drops. This was increased by one drop daily until a maximum of 15 drops were ingested. This dosage was continued until 0.5 oz. of the oleoresin had been consumed. The concentration was then increased to 1:50 and an initial dose of 10 drops administered. This was again increased by one drop daily until 15 drops were reached. This daily dose of 15 drops was continued until the content of the 0.5 oz. bottle was exhausted on September 13. During a period of 105 days, 0.5 oz. each of the 1:200, the 1:100, and the 1:50 dilutions was ingested. At the termination of this period of fractional oral therapy, a patch test with the 1:100 ivy oleoresin in corn oil was applied to the right arm. Twenty-four hours later erythema, swelling, and fine vesiculation appeared at the tested site. This response was of less intensity than those occasioned by the same dilution previous to fractional oral therapy. It was later shown that patch tests are less severe if applied one week or longer after the last oral dose.

Drops were placed in the number one capsule and ingested immediately after the evening meal. Mild gastric upsets are occasionally observed if plant oleoresins are taken when the stomach is empty. Shortly after beginning the 15-drop daily dosage of the 1:50 concentration of the oleoresin, pruritus ani developed. Although treatment was continued at the same level of 15 drops daily, this symptom disappeared spontaneously in approximately ten days.

In some persons anal pruritus becomes so intolerable that oral therapy must be discontinued temporarily. This symptom can frequently be prevented by thorough washing of the perianal area with soap and water after each bowel movement. Disappearance of anal pruritus while a patient is gradually increasing the amount of oleoresin ingested is a fair indication of reduction of cutaneous sensitivity. Disappearance of this symptom while the patient is taking increasing

dosage of the oleoresin has uniformly paralleled reduction in skin sensitivity as shown by quantitative patch tests.

Sept. 13 to Sept. 18, 1939. Period of Healing of Patch Test.—Oral treatment of the nurse was discontinued during healing of the patch test from the 1:100 ivy-corn oil dilution applied September 13. Oral dosage as low as 1 or 2 drops of the 1:100 dilution of the ivy oleoresin frequently exaggerates an existing clinical dermatitis or positive patch test in markedly sensitive patients.

I have never observed any benefit in an existing ivy dermatitis from the intramuscular injection of small amounts of the oleoresin prepared in my office (1 c.c. of 1:1,000 to 1:100,000 dilution in corn oil) or from various commercial extracts, most of which vary from 1:1,000 to 1:3,000 dilution. Before finally abandoning the phylactic treatment of ivy dermatitis with extracts injected intramuscularly, one forearm of six ivy-sensitive persons was painted with the 1:10 dilution of ivy oleoresin in acetone. No treatment was permitted. After healing of the dermatitis, the opposite forearm was painted with the same dilution of the extract. Three or four intramuscular injections of four commercial extracts were given. To avoid errors of supersensitivity, fluctuations in sensitivity, and refractory periods, the procedure was repeated in the reverse order, administering extracts intramuscularly during the first cutaneous reaction and allowing no treatment during the second. Healing time was identical in both the injected and untreated cases. When the strongest known commercial extract was employed (approximately 1:170 dilution), one volunteer complained that pruritus of the area was markedly intensified. On numerous occasions I have observed an ivy dermatitis which was exaggerated by the intramuscular injection of this extract and those of equal strength prepared in my office. I am convinced that the intramuscular injection or oral administration of weak dilutions of ivy oleoresin do not benefit an existing ivy eruption. Stronger concentrations of the extract are prone to exaggerate the dermatitis.

Sept. 18 to Oct. 16, 1939. Period of Shock Therapy.—Immediately after healing of the patch test, shock or toxic doses were administered in order to study the effect on cutaneous sensitivity. The concentration of the treatment extract was increased to 1:25 and an initial dose of 60 drops (4 capsules) given daily. This dosage was eight times the maximum daily amount previously ingested. A single dose of 5 drops of such concentration usually suffices to produce symptoms of intolerance in an untreated patient of marked sensitivity. Four days after beginning this large daily dosage, pruritus ani developed. Two days later, the anal pruritus was severe, vulval pruritus appeared, and the healed patch sites on the arms, back, and palate became erythematous and swollen. The following day an erythematous, scarlatiniform,

patchy rash developed over the trunk and extremities, and a pompholyx-like vesicular eruption appeared diffusely over the fingers, palms, and toes. In order to observe the effect of further high oral dosage in the presence of symptoms of intolerance, the nurse ingested 60 drops of the 1:25 dilution of the oleoresin daily for the following five days. At the end of this period, the skin of the entire body was fiery red with a brawny edema. The legs and arms were swollen to almost twice their normal circumference. Edema at the former patch sites was so marked that extreme vesiculation ensued. The hands and feet were covered with pompholyx-like vesicles. There was an intense erythema of the urethral orifice and surrounding mucous membrane. The anal, vulval, and general pruritus was so extreme that the subject was able to sleep only two or three hours nightly. It was at this point that oral treatment was discontinued.

That such large doses are not injurious is indicated by the fact that the blood pressure, urinalyses, blood count, and general physical findings were normal throughout this period. The intense erythema of the urethral orifice suggested that the dermatitis-producing fraction of the ivy oleoresin was excreted in the urine.

Although the nurse ingested the final 60-drop dosage on September 26, the rash did not entirely disappear until October 10. A patch test on the upper arm at this time with the 1:100 dilution of ivy in corn oil showed diffuse erythema with slight swelling. A branch of poison ivy was then gathered, and the leaves were crushed gently with the fingers. The branch with its partially crushed leaves was stroked over the arms and back of the subject for two minutes. An ivy dermatitis did not follow this contact, which may or may not have equalled an ordinary clinical exposure to the plant. The left side of the back was then gently "whipped" with a similarly prepared branch. Twenty-four hours later an erythematous, slightly edematous dermatitis appeared over the contacted area. The eruption disappeared by the morning of October 16 (five days), suggesting an irritative type of eruption.

Two types of ivy dermatitis exist—the irritative and the allergic. The milky juice of the poison ivy plant is markedly escharotic and all persons who contact this sap develop a subsequent dermatitis. I have observed many instances of the irritative type of ivy dermatitis in persons who were not allergic to the plant (failed to react to the 1:10 ivy in acetone, the bruised leaf, and plant meal on patch test). Irritative eruptions have usually been encountered in children after the playful whipping with branches of ivy. In adults it has been observed following the climbing of ivy-covered trees by pecan threshers and night hunters and after the pulling of vines and the grubbing of roots in the clearance of land. Other plants which are prone to cause irritative

reactions in both man and animal, but which are very infrequent sensitizers, are many species of spurges and several of the true buttercups *(Ranunculaceae)*.

Oct. 17, 1939, to Jan. 8, 1940. Period of Tolerance for Massive Oral Dosage.—It was previously demonstrated that persons who developed a shock reaction following the ingestion of a single large or toxic dose of the oleoresin could ingest with impunity similar large amounts of the oil after all symptoms of intolerance from the initial shock dose had disappeared.[1] This refractory period of oral tolerance has lasted at least six months, the longest interval tested to date. In order to determine the degree of oral tolerance of this nurse after her extreme cutaneous shock manifestations, she was given increasingly large amounts of the oleoresin at three-day intervals.

The three-day interval was chosen because it had been proved previously that ivy oleoresin ingested daily has a cumulative effect. After a single large dose of ivy oil by mouth, traces of the dermatitis-producing fraction of the oleoresin could be demonstrated in the urine through the fifth day, although the maximum output was usually within the first forty-eight hours.

The numbers of capsules of 15 drops each of the 1:25 dilution of the oleoresin ingested by this subject at each three-day interval were 4, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 22, 25, 30, 35, 40, 45, 50, and 55. The only symptom of intolerance observed during the entire period was transient pruritus ani, dermographism, and a mild toxic erythematous rash which appeared about the middle of this treatment stage (14 and 15 capsules) and disappeared spontaneously after a few days although oral treatment was not interrupted. During two and one-half months, 6,870 drops (approximately 8.5 oz.) of the 1:25 dilution of the oleoresin were ingested. Employing the maximum amount we have ever injected (1 c.c. of the 1:100 dilution) and giving treatments twice weekly, it would have taken approximately ten years to have administered this amount of oleoresin intramuscularly. Had commercial extracts been employed, known concentrations of which vary from approximately 1:170 to 1:3,000, it would have required from sixteen to three hundred years to have administered a similar amount of the oil.

Repeated patch tests with the 1:100 dilution of ivy oleoresin in corn oil applied during this period of massive oral therapy produced erythema and slight swelling but did not alter the cutaneous sensitivity. Also, this extreme oral dosage did not appreciably increase or decrease sensitivity. During this entire period the nurse showed no systemic toxic effects, and the blood pressure readings, urinalyses, and blood counts were normal.

A specimen of urine was collected twelve hours after the final dose of fifty-five capsules. A drop of this specimen was allowed to dry on

four separate areas of her forearms. Twenty-four hours later, a mild erythema developed at all sites. These reactions were almost identical with those evoked at this time with the 1:100 dilution of ivy oleoresin in corn oil. Drops of the specimen placed on untreated ivy-sensitive patients elicited frankly vesicular patch reactions. An artificially sensitized assistant in my office developed an erythematous and finely vesicular dermatitis over the dorsa and sides of the fingers after handling this urine.

Although the nurse's skin was mildly sensitive to her own urine, reduction in skin and mucous membrane sensitivity is indicated by the fact that during the shock reaction the ingestion of four capsules daily caused intense erythema of the urethral orifice and surrounding mucous membrane and skin, whereas the extreme dosage of fifty-five capsules caused no reaction at these sites. It was later shown that the excitant of poison ivy is not the oleoresin but a dialyzable urine- and water-soluble fraction of the oil.[3]

Jan. 9 to Jan. 23, 1940. Rest Period.—From January 9 to January 23, no oral treatment was given and no cutaneous patch tests were done in order to determine whether or not a temporary rest, followed by massive oral dosage, would break a refractory period of oral tolerance.

Jan. 24 to Jan. 30, 1940. Period of Massive Oral Dosage.—The nurse ingested daily twenty capsules (300 drops) of the 1:25 dilution of ivy in corn oil for one week. No symptoms of intolerance of any type developed. At this time I ingested 5 c.c. (ten capsules) of the 1:10 ivy dilution. A specimen of my urine collected twelve hours later evoked a negative patch response on this subject, but frankly positive reactions on two untreated ivy-sensitive volunteers. A rest period did not alter skin sensitivity or oral tolerance.

Jan. 31 to Feb. 13, 1940. Period of Patch Testing.—Since many persons nonsensitive to ivy can be artificially sensitized to this plant by a single patch test with a concentrated extract of its oleoresin, persons hyposensitized to ivy by oral therapy might theoretically have their degree of sensitivity return to the former high level by a single clinical exposure. If ordinary contact with the plant will revert the subclinical sensitivity of a hyposensitized person to a clinical sensitivity, then treatment must be continued throughout the growing season of poison ivy and repeated annually.

On January 31, the nurse was patch tested with extracts stronger than the dilution arbitrarily employed by me when testing clinical sensitivity (1:100 ivy oleoresin in corn oil). The large number of patch tests were also applied to determine if positive patch reactions would cause loss of oral tolerance for the oleoresin. The 1:10 dilution of the oleoresin in acetone is not a cutaneous irritant, as proved by the routinely negative patch responses on newborn infants, but it does evoke positive

patch reactions in persons who do not develop a dermatitis following ordinary exposure to the ivy plant (subclinical sensitivity).[2] The testing material and mode of application were identical with those employed before oral therapy was instituted. Additional tests were made with acetone dilutions of oleoresins supplied by H. L. Graham and Eli Lilly and Company. The dilutions employed, sites tested, and the results were as follows:

1. 1:10, Acetone. Forearm. Redness, swelling, and fine vesiculation.
2. 1:10, Acetone. Forearm. Redness, swelling, and fine vesiculation.
3. 1:100, Acetone. Forearm. Diffuse redness, slight swelling.
4. 1:100, Acetone. Forearm. Diffuse Redness, slight swelling.
5. 1:100, Acetone. Upper arm. Diffuse redness, doubtful swelling.
6. 1:100, Ether. Forearm. Annular erythema at patch margin.
7. 1:200, Ether. Forearm. Negative.
8. 1:400, Ether. Forearm. Negative.
9. 1:1,000, Acetone. Forearm. Punctate erythema fourth day.
10. 1:10,000, Acetone. Forearm. Negative.
11. 1:20,000, Acetone. Forearm. Negative.
12. 1:10, Acetone. Back. Redness, doubtful swelling.
13. 1:10, Acetone. Back. Doubtful reaction.
14. 1:100, Acetone. Back. Negative.
15. 1:100, Acetone (fresh root oil). Back. Redness, swelling, doubtful vesicles.
16. 1:100, Ivy leaf oleoresin in corn oil, covered 24 hours. Arms. Mottled erythema.

Previous to oral therapy, all the above dilutions caused frankly vesicular patch reactions. The marked variations in reactions evoked by the ether and acetone extracts could not be explained. The most intense responses had always been elicited on the forearms, which had previously been the site of dermatitis from clinical exposure and patch tests. Prior to attempted desensitization, some fifty patch tests with the 1:10 ivy in acetone had been applied to these areas in washing experiments.[2] At that time, the application of 1:10 ivy in acetone to the forearms for as short an interval as ten seconds elicited positive, though reduced, responses even when the forearms were thoroughly washed with soap and water, acetone, ether, and carbon tetrachloride for several minutes or longer. Solutions of ferric chloride and potassium permanganate were found of no value in preventing or mitigating an ivy dermatitis after clinical exposure or patch tests.

All above enumerated patch sites except those occasioned by the 1:10 leaf oil and the 1:100 root oleoresin had practically healed in five days. At this time, 15 capsules (225 drops) of the 1:25 leaf oleoresin were ingested daily for four days. There was no visible flare-up of patch sites,

but the nurse complained of increased pruritus of the healing areas. A large number of patch tests had not caused a loss of oral tolerance.

Eleven days after the above tests, a patch application with the 1:100 ivy oleoresin in corn oil applied to the supersensitive forearm provoked a mottled erythema. A large number of patch tests had failed to increase skin sensitivity.

The most accurate method of gauging the reduction in sensitivity attained from oral therapy consists in choosing for the testing sites areas which have not previously been the seat of an ivy dermatitis from clinical exposure or patch applications. Clinical ivy dermatitis rarely involves the back. Our most uniform test results have followed employment of one side of the back for quantitative testing prior to oral therapy and, one week or longer after the last oral dose, similar testing of the opposite side. Conventional patch sites such as the arms and forearms often show patchy variations in sensitivity due to supersensitivity of previously affected areas, which, in ivy dermatitis, is often in streaks. Healed patch sites may remain hypersensitive at least ten years after the original dermatitis.

Feb. 14 to April 10, 1940. Root Oleoresin Orally.—On February 14, oleoresin extracted from roots was substituted for the leaf oil, and the concentration was increased to 1:10. After many quantitative patch tests on ivy-sensitive volunteers, it was estimated that this oleoresin, extracted from recently grubbed roots, was approximately four times as potent as the leaf oleoresin the nurse had recently been ingesting.[3] One capsule of the 1:10 root oil was therefore equal to ten capsules of the 1:25 leaf oleoresin (2.5×4). One capsule of the 1:10 root dilution was ingested daily. On the fourth day after beginning this dosage, a mild, patchy, erythematous, toxic, medicamentosa-type rash appeared over the face, trunk, and extremities. There was no flare-up of patch sites or pruritus vulvae, but there was moderate pruritus ani. Treatment was discontinued and the symptoms of intolerance disappeared in four days. Slight loss of oral tolerance for ivy had apparently occurred. To determine if cutaneous sensitivity had also increased, the nurse was patch tested again with all the dilutions previously applied. The results indicated no loss of cutaneous protection. During the presence of the dermatitis medicamentosa eruption, she was also tested with the 1:100 ivy oleoresin in corn oil (1) at a site of unaffected skin; (2) over a patch site which had been healed seven days; and (3) over an erythematous area of dermatitis medicamentosa. Tests 1 and 2 were of equal intensity, showing mottled erythema without swelling. The site of Test 3 showed erythema, swelling, and fine vesiculation. Therefore, an area of existing dermatitis medicamentosa is more sensitive to patch test than an area of unaffected skin. At this time, areas of dermatitis medicamentosa and unaffected skin did not show metallergic reactions to other

weed oleoresins. Metallergic reactions are very frequently encountered in untreated, plant-sensitive persons if healed patch sites are tested with many nonspecific oils. Such reactions are very rarely encountered in plant-sensitive persons who have received prolonged oral therapy.

That oleoresin extracted from the roots and leaves of the same plant may differ is indicated by skin reactions briefly reported before this association last year. A housewife, with a patchy eczema of the hands, gave frankly vesicular patch reactions to carrot roots but negative responses to the crushed stems and leaves of the plant.[4]

One week after the nurse's toxic dermatitis medicamentosa eruption from the root oleoresin had disappeared entirely, a patch test with the 1:100 ivy leaf oleoresin in corn oil applied to the upper arm showed a very doubtful mottled erythema on the fourth day. The following morning, no trace of the patch could be found.

Daily treatment with 15 drops of the 1:10 root oil was again instituted. After two capsules, a mild, patchy dermatitis medicamentosa again appeared. Treatment was interrupted, and the rash disappeared in four days.

Treatment was again instituted with the same daily dosage. On the fourth day, the nurse complained of pruritus ani and pruritus vulvae. Patch tests with a specimen of her urine produced frankly vesicular reactions on three untreated ivy-sensitive persons, but no response on several areas of her own skin. Treatment was not interrupted. A toxic, erythematous, blotchy eruption appeared over the body on the seventh day. Although the patient continued each day to ingest one capsule of the same root oil concentration, the pruritus vulvae, pruritus ani, and toxic eruption disappeared spontaneously in approximately one week. This daily dosage was continued for thirty-five days (to April 10) without the slightest evidence of symptoms of intolerance. During this entire latter period, she ingested 15 drops of the 1:10 root oleoresin with as much impunity and inconvenience as one would experience after swallowing an equal amount of an inert oil.

April 11 to April 24, 1940. Period of Indirect Skin Testing.—On April 11, succulent poison ivy leaves were rubbed between my fingers for several minutes. Within fifteen minutes the palmar surface of the digits was stained a deep black, proving the presence of a large amount of ivy oleoresin. The patient's right arm was then vigorously rubbed for one minute with my contaminated fingers. My hands were then washed with soap and water for one minute, and her opposite arm was similarly rubbed. The arm rubbed with the unwashed hands developed an erythema after forty-eight hours. This reaction disappeared in four days. This massive exposure produced similar reactions on four patients proved subclinically sensitive to ivy by direct contact with the plant on field trips. A dermatitis did not develop at the site rubbed with the

washed hands. When the arms of two clinically sensitive patients were similarly rubbed with the washed hands, a vesicular dermatitis resulted.

It should be remembered that poison ivy dermatitis over the face, body, and genitals is usually caused from contact with the patient's own contaminated hands and rarely from direct contact with the plant. The thickness of the epidermis of the palms and palmar surface of the fingers usually inhibits a reaction at these sites. The manual transference of the oleoresin to other areas of the body where the epidermis is thin results in the typical vesicular ivy reaction. Accidentally contaminated hands seldom contain enough of the oleoresin to cause the black stain exhibited when leaves are vigorously crushed with the fingers as in the above experiment. On numerous occasions I have pressed an ivy leaf between the thumb and index finger with only enough pressure to slightly bruise the leaf and leave no residual stain. When ivy-sensitive persons were then stroked with the fingers over multiple areas of the body, vesicular lesions in streaks resulted in the first few contacted sites after an average latent period of twenty-four hours. Those areas contacted last, after most of the oleoresin had been rubbed from the hands, often showed diminished reactions, and the latent period often was not constant for the individual, but delayed four or five days. This apparently accounts for new lesions of ivy dermatitis appearing several days following a proved single exposure. The careful tracing of exposures to poison ivy indicates that a relatively high percentage of the cases of ivy dermatitis do not result from direct contact with the plant, but follow indirect contact with such intermediary contaminated objects as hands of other persons, pets, golf clubs, shoes and other types of clothing, garden and farm tools, etc.

The appearance of an ivy dermatitis with no history of actual contact with the plant has given rise to the fallacious belief among both physicians and laymen that one may develop an ivy dermatitis by merely going into the vicinity of the plant. This belief has been proved erroneous on repeated occasions by actually taking extremely sensitive persons to within a few feet of the plant. Ivy was carefully collected to avoid any injury to the fragile epidermis of the leaves, and the forearms of the volunteers gently stroked with the leafy branches. In not a single instance did ivy dermatitis develop. Since the epidermis of the ivy leaf contains no resin ducts, injury to the leaf covering is necessary for actual contact with the sap. Ivy oleoresin is not volatile and therefore is not wind-borne. Boiling over a flame does not materially alter its antigenic potency.[3] There are no resin ducts in the outer third of the stamens or in the anthers of the ivy flowers so the pollen could not contain the antigenic oil. One gram of uncontaminated ivy pollen was tediously collected by pulling out the anthers of the fully developed flowers with fine forceps. Patch tests with this pollen and its con-

centrated ether extract failed to evoke skin reactions on highly sensitive volunteers. Pollen collected in the conventional way, and also by shaking the flowers over a sieve, was always contaminated with fine ivy particles and routinely resulted in extreme reactions on the same subjects. Therefore, actual contact with ivy oleoresin, whether this be direct or indirect, is necessary for the development of a subsequent ivy dermatitis.

Eight days after development of ivy dermatitis on the nurse's arm from contact with my unwashed hands, covered twenty-four-hour patch tests with five well-known commercial ivy extracts were applied to the opposite arm. All test sites remained negative. The steering wheel of the family car was then contaminated with the ivy oleoresin in the same manner as before oral therapy. Manual contact with the wheel was not followed by a dermatitis. Previous to oral therapy, such indirect contact by the nurse resulted in a widespread vesicular dermatitis.

Patch tests applied to the back at this time showed a mottled erythema at the site tested with the 1:10 acetone leaf extract. Higher dilutions were entirely negative. Similar tests applied to the left forearm, a site which had always shown the most severe reactions, evoked redness and slight swelling at the area tested with the 1:10 acetone dilution. The 1:100 acetone extract evoked slight redness but no swelling. Higher dilutions were entirely negative. The 1:100 ivy oleoresin in corn oil and higher dilutions applied to the upper arm evoked no reactions.

To test loss of oral tolerance, the nurse was then given one capsule (15 drops) daily of the 1:10 root oleoresin in corn oil for five days. The final dose was ingested April 24. No symptoms of intolerance developed. A localized dermatitis from massive indirect clinical exposure was not followed by an increase in skin sensitivity or a loss of oral tolerance.

April 25, 1940. Clinical Exposure to Ivy.—On this date the subject, dressed in nurse's uniform with short sleeves and wearing anklets, and my two sons, who had previously been desensitized to poison ivy, were subjected to a clinical exposure to this plant. For a period of thirty minutes they walked through trailing ivy vines, picked leaves, and broke low-hanging branches. The leaves of the broken branches were then bruised and freely handled. The nurse held the branches in her bare arms so that the leaves would touch her face and neck. They were then stroked over the arms and faces of all three subjects. The two boys were then instructed to rub their supposedly contaminated fingers on the nurse's face, neck, and arms. All three patients wore the same clothes for twenty-four hours, and bathing was not permitted during this period. This contact with the plant was considered equal to, or greater than, an ordinary clinical exposure.

Forty-eight hours later, the nurse developed a slightly swollen erythema of the left cubital fossa and left wrist with three erythematous

streaks over the forearm. Ten widely scattered, pinhead-sized, pruritic papules were observed on the right forearm the following day. On the fourth day an ephemeral erythematous patch appeared on the right knee. Vesiculation did not occur at any of the affected sites, and no other portions of the body were involved. Complete healing of all sites occurred in from three to six days. Had exposure not been known, a clinical diagnosis of ivy dermatitis could not have been made with certainty. According to her history, previous attacks of ivy dermatitis had been widespread and characterized by intense vesiculation and marked swelling, usually requiring confinement to bed for a week or longer. Only on one occasion was actual contact with the plant known. Subsequent attacks were said to have followed visits to ivy-infested districts, although direct contact with the plant was purposely avoided. If the above intentional exposure can be considered an ordinary one, then hyposensitization to ivy had followed oral therapy although desensitization had not occurred.

Fig. 1.—Photograph taken during first clinical exposure after institution of oral therapy (April 25, 1940). The nurse is standing in poison ivy and holding broken branches of the plant in her hand.

Prior to oral therapy, my two sons were also repeatedly patch tested over the back and forearms with serial dilution of ivy leaf oleoresin in acetone. The highest dilutions to which they regularly reacted at both sites were 1:200 and 1:500, respectively. The 1:10 dilution always occasioned frankly vesicular responses. Both boys had suffered one or

more mild clinical attacks of ivy dermatitis. During a period of three months each ingested a total of 1 oz. of the 1:10 leaf oleoresin and 1 oz. of the 1:10 root oleoresin in corn oil. One week following the last oral dose, patch tests with the 1:10 and higher dilutions evoked no reactions. Multiple patch tests with the 1:10 acetone extract applied three times weekly for one month failed to resensitize them. Following the above clinical exposure, neither developed any evidence of an ivy dermatitis and patch tests with the 1:10 and higher dilutions remained entirely negative. The term "resensitize" is employed since acetone extracts stronger than 1:10 may act as primary irritants.[2]

Fourteen days following the nurse's clinical exposure, patch tests were made with fresh oleoresin extracted from green leaves collected during the full flowering stage of the plant. Such oleoresins are more antigenic and markedly more irritating than similar oils extracted from leaves dried from two weeks to three years. Applications on the back showed redness and swelling at the site tested with the 1:10 acetone dilution. The 1:100, 1:200, and 1:400 dilutions showed erythema without swelling after forty-eight hours. Tests with higher dilutions were negative. On the upper arms, the 1:100 ivy in corn oil and all higher dilutions elicited no reaction. On the volar surface of the forearms, the 1:100 ivy in oil caused redness and isolated papules. The mild dermatitis which followed clinical exposure had not increased skin sensitivity.

Four days later the nurse was subjected to a second clinical exposure. The procedure was exactly the same as during the first clinical test, except on this occasion the indiscriminate picking of ivy leaves and the breaking of branches were not permitted. No evidence of dermatitis followed this clinical trial.

On May 13, oral therapy of one capsule daily of the 1:10 root oleoresin was again instituted. To date, no symptoms of oral intolerance have arisen. She will continue to ingest this dosage until complete desensitization has been achieved or until it is found that further reduction in skin sensitivity is not possible.

COMMENT

Some forty selected ivy-sensitive persons have, to date, been treated by either shock or prolonged fractional oral therapy. Reduction in skin sensitivity, as shown by quantitative patch tests, has occurred in all volunteers thus treated. Repeated patch tests on many of those hyposensitized by shock therapy caused a reversion of the sensitivity to the former high level. In others, numerous positive patch tests did not materially increase sensitivity. Repeated patch testing has not, to date, appreciably altered reduced sensitivity which has followed prolonged fractional therapy.

Not until a large number of treated ivy-sensitive patients are clinically exposed to the plant will we have actual proof that sensitivity can be reduced regularly to the point where an ordinary exposure will not be followed by a dermatitis. Such clinical tests will indicate whether a reduced sensitivity is temporary or permanent and whether or not single or repeated exposures to poison ivy will revert a subclinical to a clinical sensitivity. The outcome of such exposures will guide future therapy. Until we have some patch test procedure which accurately approximates the amount of oleoresin contacted during an ordinary exposure to the plant, clinical trials will be necessary. The testing of clinical sensitivity to weeds has been a much simpler procedure since few weed oleoresins are primary skin irritants.[2]

Present data indicate that an individual of average sensitivity to ivy must ingest the equivalent of 2 c.c. of a potent leaf oleoresin to reduce sensitivity from a clinical to the subclinical level. By increasing the oral dosage as rapidly as the tolerance of the patient permits, such an amount can usually be ingested in a period of three months or less.

Due to local reactions, we have rarely been able to administer intramuscularly as much as 1 c.c. of the 1:100 dilution of a potent ivy oleoresin in an inert oil or alcohol. Presuming that such a high dosage could be tolerated, it would require some 200 injections to administer 2 c.c. of the ivy oleoresin subcutaneously. Were commercial extracts employed, known strengths of which vary from 1:170 to 1:3,000, and were maximum doses of 1 c.c. injected twice weekly, it would require from three and one-half to sixty years to administer the required amount intramuscularly. Although administered as recommended in the advertising literature (two to four injections), the various commercial ivy extracts have, in my hands, never endowed the recipient with the slightest reduction in skin sensitivity, as shown by subsequent quantitative patch tests and clinical exposures.

Quantitative patch tests on persons of known sensitivity have proved that the commercial alcoholic dilutions of poison ivy are far less antigenic than their labeled strength would indicate. Such preparations contain from 5 to 90 per cent water. Spain and Cooke[5] observed that ivy extracts containing as little as 5 per cent water deteriorated rapidly. Four of the five proprietary specimens repeatedly checked by me showed water content greater than 20 per cent. These extracts failed to produce skin reactions on highly sensitive persons. When evaporated to 1 per cent of their original volumes, skin responses ranging from completely negative to very doubtful were evoked. Water extracts of plants completely deteriorate in from one month to six weeks.[2] Many batches of poison ivy extract prepared with dilute alcohol probably remain on the druggists' shelves until their antigenic potency has been materially re-

duced or completely lost. In attempted hyposensitization to poison ivy, a potent and stable extract should be prescribed.

SUMMARY

1. A person extremely sensitive to poison ivy was given varying amounts of the oleoresin of this plant orally during a period of approximately ten months.

2. The oleoresin proved toxic to the skin and, in a lesser degree, to the mucous membrane.

3. Massive oral doses, given experimentally and not recommended for routine oral treatment, were otherwise harmless for blood counts, urine examinations, blood pressure readings, and general physical findings remained normal throughout the treatment period.

4. Oral therapy resulted in hyposensitization yet desensitization did not occur.

5. Repeated positive skin tests and two clinical exposures failed to revert the reduced skin sensitivity to the former high level of allergy to the plant.

REFERENCES

1. Shelmire, Bedford: Contact Dermatitis From Vegetation. Patch Testing and Treatment With Plant Oleoresins, J. South. M. A. **33**: 337, 1940.
2. Shelmire, Bedford: Contact Dermatitis From Weeds; Patch Testing With Their Oleoresins, J. A. M. A. **113**: 1085, 1939.
3. Shelmire, Bedford: Nature of the Excitant of Poison Ivy Dermatitis, Arch. Dermat. & Syph. **42**: 405, 1940.
4. Shelmire, Bedford: Allergic Reactions to Plants. Symposium on Allergic Dermatoses, J. ALLERGY **11**: 59, 1939.
5. Spain, W. C., and Cooke, Robert A.: Dermatitis Venenata; Observations Upon the Use of a Modified Extract From Toxicodendron Radicans, J. Immunol. **13**: 93, 1927.

MEDICAL ARTS BUILDING

DISCUSSION

DR. C. MALONE STROUD, St. Louis.—Dr. Shelmire's theme opens a new avenue of investigation. I am glad that he mentioned the fact that many plants are poisonous. In the administration of oleoresins, the toxicity should be kept in mind because there are so many poisonous plants. A monograph by Muenscher entitled "Poisonous Plants of the United States" mentions more than one thousand varieties exhibiting some form of toxin. Some of them act as toxins on the brain, spinal cord, or heart. Others act as purgatives; some act as abortifacients; some are merely irritants. Others cause photosensitization, and many are cyanogenetic. There seems to be no reason why a plant which is toxic for man or for animals could not also act as an allergenic agent. There is obvious reason, however, why species of questionable toxicity should not be given as a therapeutic agent.

An interesting difference between results of oral therapy and results of parenteral therapy is the fact that oral therapy in sufficient dosage reduces the activity of the skin, while administration by subcutaneous or intramuscular therapy does not. For instance, we have seen patients

whose dermatitis was caused by ragweed oil improve by injection therapy, but in whom the patch test with ragweed oil remained strongly positive. It seems to me that a great deal more work should be done to determine optimum dosage. In St. Louis, we have had little experience in treatment with ivy oil. Many of us, however, have had excellent results from parenteral treatment with ragweed oil. Dr. Shelmire mentions the fact that an area of dermatitis medicamentosa was tested with ivy oil and was found to be more sensitive than other areas. This is in accord with our observation that existing dermatitis from any cause may lower the threshold of irritability of the skin. Another observation that he makes which is of interest to me is that urine of a patient who had had massive doses of ivy oil contained the antigenic substance. This, it seems, would indicate that the causative factor is water-soluble. It is well known that water causes deterioration of the antigenic factor of oleoresin of plants, but it seems likely that an aqueous extract could be used for treatment instead of an oily extract.

Dr. Harvey Black, Dallas.—I have been one of Shelmire's victims, sometimes wittingly and sometimes unwittingly, as has just been described. There are one or two things that are outstanding, I think, about this type of work. To my mind, one is the very definite evidence of the fact that Dr. Shelmire has been able to hyposensitize, at least, these persons so that they can stand what I think is an unusual amount of clinical exposure. He has been very modest and very conservative in his statements of what they can take. The exposure these patients have undergone has been, in many instances, a great deal more than one would receive by merely going through the woods and coming into casual contact with ivy. These persons have had contact with ivy with very little evidence of any involvement at all.

One thing that stands out very strikingly, I think, is the fact that these patients require treatment very much in the same manner as we give desensitizing or hyposensitizing treatment in hay fever. That is, a single dose or two or three doses are of no apparent benefit whatever. We have seen a number of these patients treated satisfactorily with continued treatment over a long period of time. We have seen some patients with other similar conditions. I have one under my care who is getting treatment with Russian thistle (*Salsola pestifer*) in New Mexico and who is staying quite well on oral treatment with the oil extract. The principle is the same, of course, in all; but it takes repeated doses and they have to be continued over a long period of time. I think Dr. Shelmire's work has convinced us that the ordinary method of treatment as proposed by the pharmaceutical houses is worthless, certainly in so far as prophylaxis is concerned, and he has the conviction that it is possibly worse than useless as a phylactic method. It seems to me that the work Dr. Shelmire has done has finally convinced us that there is a tremendous field in this direction and that it has not been exploited as much as it should be. I think it is going to show us the solution not only of a large number of poison ivy cases, but also of a lot of dermatitis which has not been recognized previously.

Dr. Max Grolnick, Brooklyn.—I have had the opportunity of studying during the past few years the role of a South American plant, krameria, as an excitant of contact dermatitis. This work has not as

yet been published. Attempts were made to sensitize subjects by oral administration of krameria (a medication used orally in the treatment of diarrhea). It was possible to administer several ounces of a fluidextract of krameria, 1.0 c.c. of which contained the therapeutic constituent of 1.0 Gm. of the root of the plant. Sensitivity could not be induced. Furthermore, in subjects who had been artificially sensitized by external application of krameria, oral administration of the fluidextract in an attempt to desensitize these subjects did not cause a diminution in the patch test reaction, although a fairly concentrated solution of the drug had been taken. It is possible that I did not reach the high dosage comparable to that administered by Dr. Shelmire in his experiments with poison ivy.

In addition, I treated about a dozen subjects who had been artificially sensitized with krameria by parenteral administration of the extract in fairly concentrated solution. There was no diminution in the patch test reaction in any subject. In the latter experiment, therefore, the results in krameria sensitivity in general paralleled those obtained by Dr. Shelmire in poison ivy sensitivity.

Dr. George L. Waldbott, Detroit.—Is it not paradoxical that the oil should work so well by mouth and not by hypodermic injections? Are you not much better able to control the doses by hypodermic injections than by mouth?

Dr. Ralph H. Spangler, Philadelphia.—I would like to ask if, in the experience of Dr. Shelmire, it is primarily allergic persons who are subject to ivy poison? A year ago I was consulted in reference to a number of college girls, twenty-five or twenty-six of them, who had poison ivy. Certainly they could not all be classed as allergic persons, since the proportion of those who contracted poison ivy to those exposed was too high.

The application of ordinary gasoline cleared up the condition and acted as a preventive. It did not cure the secondary dermatitis, which healed in due course of time.

Dr. Shelmire.—According to legend and medical writings, persons have eaten poison ivy leaves in order to desensitize themselves against the plant. Such reports must be more fiction than fact unless very young or very old leaves were chewed or were liberally mixed with food, as in a sandwich. Rabbits and guinea pigs fed a meal consisting exclusively of succulent ivy leaves invariably developed a crusting dermatitis of the lips, and almost all animals so fed died within three or four days. The fresh juice of poison ivy is as escharotic as phenol, so the chewing of potent leaves by man would probably be followed by irritative lesions of the intestinal tract similar to those observed in animals.

Oleoresins extracted from fresh leaves are very irritating. Such oleoresins will usually cause redness and burning of the skin of a nonsensitive person within fifteen minutes. One reason for completely drying leaves before extraction is that such extracts retain most of their antigenic potency, but lose almost entirely their irritative tendency. Gastric and intestinal upsets have been almost entirely eliminated by employing oleoresins from leaves dried for two weeks before extracting. Leaves stored as long as four years have not lost their antigenic potency.

Oleoresins extracted from thoroughly dried leaves rarely cause irritative reactions on proved nonsensitive subjects unless kept in continuous apposition with the skin for twenty-four hours or longer.

Were it not for pruritus ani, oral hyposensitization to poison ivy would be a simple procedure. Thorough washing of the anal area and the liberal use of zinc oxide ointment have markedly lessened this symptom which has been rather marked with the 1:25 dilution, which I have been employing recently. Since, with me, hyposensitization to poison ivy has been entirely an experimental and not a treatment problem, the fluctuations in the intensity of pruritus ani have been a welcome and valuable guide in gauging reduction in cutaneous sensitivity to the poison ivy plant.

ALLERGY IN CHILDHOOD

IV. Does Heredity Determine the Age of Onset?

Bret Ratner, M.D., David E. Silberman, M.D.,
and Janet E. Greenburgh, B.S.
New York, N. Y.

Cooke and Vander Veer[1] stated that "heredity exerts a distinct effect upon the age of onset of symptoms of sensitization. If the taint is present on both sides (bilateral), the period of maximum liability is the first five years of life; if only on one side, symptoms are most likely to appear between the ages of 10 and 15 years, while the height of the curve in those cases with negative history is not reached until a still later age—20 to 25." They concluded, therefore, that the more complete the inheritance, the earlier the manifestations. The scientific accuracy of Dr. Cooke and his co-workers in publishing their extensive and complete protocols has made it possible for us to re-examine their data from a somewhat different approach.

Influence of Family History on the Age of Onset

We have classified 250 allergic children according to the presence or absence of the taint in the pedigree, and in Fig. 1 are presented the results with respect to the age of onset. In our own patients, therefore, the period of maximum liability is the first five years of life. The incidence decreases progressively in the succeeding years. Because of the limited age range of our group, it is obvious that approximately 100 per cent of the patients are sensitive before puberty.

These results are compared with figures from Peshkin,[2] Bray,[3] Cooke and Vander Veer,[1] and Spain and Cooke[4] (Table I). Our figures agree in the main with those of Peshkin and Bray, who also limited their cases to children, but they vary widely from the findings of Cooke and his co-workers, whose patients were, for the most part, adults. In children, the onset of symptoms occurs with greatest frequency in the first five years of life, and there appears to be little difference between the three groups classified according to the type of inheritance. O'Keefe[5] (Table I) made a study of 300 children with asthma, and, interestingly enough, he found that the average age of onset for the bilateral group is 4.7 years; this is actually later than that for the unilateral group, which is 4.1 years, and that for the negative group, which is 4.3 years. The lack of influence of the type of inheritance is strikingly shown in

From the Department of Pediatrics, New York University, and Children's Division, Bellevue Hospital.
Read before the Annual Meeting of the American Association for the Study of Allergy, New York, June 11, 1940.

Fig. 1. In the first year, there is a slightly greater number of cases occurring in the bilateral group, and yet the negative group is slightly larger than the unilateral. In the two- to five-year group the preponderance occurred in the unilateral and negative; the bilateral showed the smallest number. Between the sixth and eighth years, the bilateral and the negative groups are both larger than the unilateral

TABLE I

LACK OF GENETIC INFLUENCE ON AGE OF ONSET

AGE OF ONSET	GROUP	CHILDREN (%)			ADULTS (%)	
		PRESENT SERIES	PESHKIN	BRAY	COOKE AND VANDER VEER	SPAIN AND COOKE
By the fifth year	Bilateral	78	63	88	36	53
	Unilateral	83	80	80	14	21
	Negative	79	73	75	5	12
By the tenth year	Bilateral	100	88	100	66	79
	Unilateral	95	100	100	32	36
	Negative	95	97	97	18	22

O'Keefe found the average age of onset: Bilateral, 4.7 years; unilateral, 4.1 years; negative, 4.3 years.

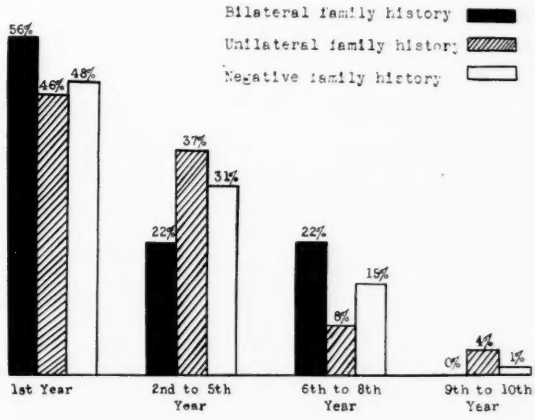

Fig. 1.—Age of onset of allergy according to the type of family history. Total sensitized by the fifth year: bilateral, 78 per cent; unilateral, 83 per cent; negative, 79 per cent. Total sensitized by the tenth year: bilateral, 100 per cent; unilateral, 95 per cent; negative, 95 per cent.

group. There is certainly no evidence of hereditary influence in our group, which is in conformity with the theory postulated by Cooke and his co-workers. Wiener, Zieve, and Fries[6] make a point of the fact that they too feel the data of Cooke and his co-workers are not entirely satisfactory for analysis of patients with the age of onset before puberty, since practically all their patients were examined in adult life. Their reasoning is that, at an advanced age, the patient could not be expected to recall the precise time of onset of allergic symptoms any more accurately than the ages at which he contracted his various childhood diseases. Our finding would seem to corroborate their criticism.

We can only conclude, therefore, that when children alone are the subject of study, the absence or presence of allergy in other members of the family appears to have little influence upon the age of onset of allergic symptoms.

THE INFLUENCE OF THE SPECIFIC ALLERGIC SYNDROME ON THE AGE OF ONSET

It seems to have been assumed that the various clinical manifestations of protein sensitization are equivalent in all respects, and in arriving at conclusions with regard to the age of onset no distinction has been made between them. Yet, a graph reproduced from Bray (Fig. 2) shows that differences exist in the curves representing the ages of onset of the various allergic syndromes. Hay fever, it will be noted, presents a very different aspect in that it is less common in the first decade and the curve ascends and reaches its height in the twenty- to twenty-nine-year interval. Rackemann[7] also pictures this difference which he found between hay fever and extrinsic asthma. The onset of hay fever may occur at any age; however, the fact that it is most frequent between the ages of 20 and 40 is also noted by Brown,[8] Markow and Spain,[9] Huber,[10] Clarke and Leopold,[11] and others.

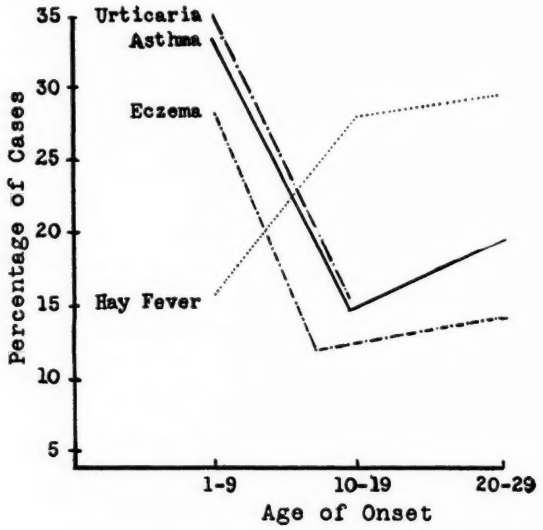

Fig. 2.—Influence of the allergic syndrome on the age of onset. (Graph taken in part from Bray, Recent Advances in Allergy, ed. 2, P. Blakiston's Son & Co. p. 43.)

A careful perusal of the painstaking protocols of Cooke and his coworkers reveals that the overwhelming majority of their patients suffer from hay fever, either pure or in combination with other syndromes. If it is true that hay fever does not commonly occur in the first decade, we should expect but a small number of their entire series of cases to

fall into the period up to five years; this is actually so. Of a total of 500 cases presented by Cooke and Vander Veer, only fifty-eight had their onset in this period; of the 462 cases of Spain and Cooke, this is true for just ninety-one. Nor are we surprised to find that their cases show a different distribution from our cases, in which just twenty-four patients, or approximately 10 per cent, suffered from hay fever. Wiener and his co-workers found that in sixty-six families there were ninety-four allergic children, nine, or approximately 10 per cent, of whom had hay fever. We examined the protocols of Spain and Cooke and discovered that irrespective of the type of inheritance 75 per cent of the patients whose age of onset fell between 0 and 5 years suffered from asthma, either pure or associated with other allergic symptoms. Only 34 per cent of those having their age of onset in the first period suffered from hay fever either alone or in conjunction with asthma, atopic coryza, or urticaria.

According to Cooke and his co-workers, the largest number of patients with a negative history fall into the group whose age of onset is between 20 and 25 years. If, therefore, this group is composed largely of hay fever patients, we would expect to find that hay fever patients more frequently have a negative family history than do patients with other clinical manifestations of allergy.

Markow and Spain state that an allergic history in hay fever cases could be elicited in only forty-five patients, or 23 per cent, of the 200 cases studied. Thirty per cent of the 300 patients studied by Huber had relatives with symptoms of allergy. Rackemann gives an incidence of 35 per cent.

Piness and Miller[12] had the unique experience of studying the onset of hay fever in two comparatively young communities with an atmosphere heavily laden with pollen. A history of positive heredity was obtained in only 30 per cent of the cases. The great majority of patients began to have hay fever only after moving to these vicinities, most of them within the first few years of their residence. Heredity seemed to play but little part in determining the interval which elapsed between the time that residence was taken up in the community and the onset of hay fever; persons who had a negative family history developed hay fever after a short residence, and persons with positive family history did not develop it until after ten to fifteen years of exposure. This was so striking to these authors that they felt forced to consider the possibility that even nonallergic persons, so-called, may have become sensitized by the superabundance of pollen. It would seem that the large number of children from 1 to 10 years of age developing hay fever, as Piness and Miller point out, is the result of an unusual contact at a particularly vulnerable period in life rather than of an inherited susceptibility.

COMMENT

We present for consideration the proposition that the preponderance of hay fever cases in data pertaining to adults has led to the existing impression that patients with negative histories have a later age of onset. The actual state of affairs is that the onset of hay fever occurs later and that patients with hay fever present a lower incidence of positive family histories. Other clinical forms may also occur at any period, but from our data we find that eczema occurs earliest; the average age of onset of asthma and urticaria is intermediate. Persons who have their age of onset after puberty are, for the most part, hay fever sufferers.

Wiener, Zieve, and Fries postulated a new theory to explain the mode of inheritance of allergy. They believe in the existence of two sorts of allergic persons having a bimodal distribution when classified according to age of onset; namely, those allergic persons whose symptoms begin before puberty and those persons who are normal transmitters or develop allergic diseases after puberty. The viewpoint herein considered might have led them to the conclusion that the bimodal distribution is caused more by extrinsic factors than by genetic attributes.

As Rackemann aptly states, so far as any underlying mechanism is concerned in the age of onset, the clinical manifestations depend solely upon the immunologic process involved and the manner and age at which a sensitiveness to the particular allergen occurs.

Our viewpoint is further supported by the recent observations of Clarke and Leopold, who found that the effects of exposure to pollen and pollen concentration on the age of onset of hay fever are important factors irrespective of heredity.

CONCLUSIONS

1. From the analysis presented, it is seen that histories on the age of onset before puberty obtained from adults are not entirely satisfactory.

2. The variation in the age of onset in patients with a positive family history and those with a negative history will be found to be negligible if the data are commensurable.

3. If patients differ in the age of onset of allergic syndromes, it is more likely that this is caused by variations in the type of the allergen and allergic syndrome rather than by genetic differences.

REFERENCES

1. Cooke, R. A., and Vander Veer, A., Jr.: Human Sensitization, J. Immunol. 1: 201, 1916.
2. Peshkin, M. M.: Asthma in Children. IV. Hypersensitiveness and Family History, Am. J. Dis. Child. 36: 89, 1928.
3. Bray, G. W.: Recent Advances in Allergy, ed. 2, Philadelphia, 1934, P. Blakiston's Son & Co.

4. Spain, W. C., and Cooke, R. A.: Studies in Specific Hypersensitiveness. XI. The Familial Occurrence of Hay Fever and Bronchial Asthma, J. Immunol. **9**: 521, 1924.
5. O'Keefe, E. S.: An Analysis of 300 Cases of Asthma in Children, New England J. Med. **214**: 62, 1936.
6. Wiener, A. S., Zieve, I., and Fries, J. H.: The Inheritance of Allergic Disease, Ann. Eugenics **7**: 141, 1936.
7. Rackemann, F. M.: Clinical Allergy, New York, 1931, The Macmillan Company, p. 139.
8. Brown, A.: Diagnosis and Treatment of Seasonal Hay Fever, M. J. & Rec. **123**: 301, 1926.
9. Markow, H., and Spain, W. C.: Ragweed Hay Fever, J. ALLERGY **1**: 414, 1930.
10. Huber, H. L.: A Critical Analysis of the Information Obtained From Hay Fever Sufferers, J. ALLERGY **2**: 48, 1930.
11. Clarke, J. A., Jr., and Leopold, H. C.: Effect of Pollen Contact Upon the Age of Onset of Hay Fever, J. ALLERGY **11**: 494, 1940.
12. Piness, G., and Miller, H.: An Unusual Opportunity to Make an Allergic Study of an Entire Community With the Etiology and Results of Treatment, J. ALLERGY **1**: 117, 1930.

50 EAST 78TH STREET

DISCUSSION

DR. GEORGE PINESS, Los Angeles.—Dr. Ratner presents a subject this morning that has been discussed time and time again. After having spent a considerable amount of time on this same subject, I have come to the conclusion that the importance of heredity is of an academic nature only and that, from the practical standpoint, one does not depend upon heredity for a diagnosis or for the manner of treatment which is to be given.

One of the reasons for this discussion is to try to determine why persons are allergic, but this will not bring forth the answer because very few people have any idea about their geneology, and the reports of large percentages or small percentages of positive family histories must be dependent entirely upon the individual who takes the history.

One will observe that the class of people dealt with is a factor in obtaining positive and negative histories. In the clinics where the various races are mixed and where illiteracy is great, there are fewer positive replies.

The results of the survey that we made in a study of two communities revealed the lack of importance of the family history from the clinical standpoint and also the great importance of treating the individual and not his family history. We found in this study that the percentage was only 30 in a group class of educated persons—mostly executives with college education and employees who were above the average as far as intelligence and education were concerned.

Age onset in relation to the history is of no importance clinically. I am convinced that, in a large group of cases, a study of the onsets will prove that the greater number occur in the first two decades of life and from that point gradually slope down to a plateau. It is safe to say that as age increases, the frequency number of cases decreases.

The final conclusion should be that heredity is of no importance in the treatment of the allergic patient.

DR. MILTON B. COHEN, Cleveland.—This subject has been discussed extensively for many years and is still far from being solved. There are two important reasons which account for failure. The first is that

there are no satisfactory criteria for a family history. The second is that we now recognize only well-developed clinical allergy and include in our series only persons who have it in well-recognized form. As we study any well-developed disease, we learn to recognize less typical cases and gradually to discover earlier and earlier variations from normal caused by the disease process. Our goal is to unmask the disease in its preclinical forms.

When and if we succeed in doing this for allergic conditions, we may be able to establish objective criteria on which to base our statistics. We may then be able to determine the importance of heredity.

EXPERIMENTAL REPRODUCTION OF RESPIRATORY MOLD ALLERGY

LEONARD H. HARRIS, M.D.
ELYRIA, OHIO

SUBSTANCES which give positive skin tests are not necessarily of clinical importance in the patient giving the reaction. This accounts for much of the disagreement as to the relative importance of molds as allergens. The importance of mold reactions is particularly obscured at times because allergy to pollens not infrequently coexists with mold allergy.

This investigation was undertaken in an attempt to evaluate skin reactions to *Alternaria* by the experimental reproduction of respiratory allergy in a group of patients reacting to this mold.

Several factors may be of aid in evaluating clinical sensitivity to molds:

1. The typical mold history has been emphasized by Feinberg[1] and others. This is probably the most outstanding aid to the diagnosis. Typically, these patients complain of:

(a) Summer hay fever or asthma that does not fit in with the pollen season, often lasting from April to December; (b) failure to clear up with the frost or not until the snow falls; (c) symptoms during the pollen-free period in July and early August; (d) failure of previous pollen therapy; (e) tendency to be worse in dry, windy, hot weather preceded by rain; (f) history of acute allergic attacks occurring in special environments, such as in barns, haylofts, strawstacks, and musty damp rooms or basements, or during sleigh rides, threshing, and circuses.

A typical mold history, if obtainable, is of great aid, but as often as not, patients' histories are unreliable and an objective aid to the evaluation of mold sensitivity is desirable.

2. Transferable reagins to various molds may or may not be present in the individual case. Moreover, their presence does not necessarily prove clinical sensitivity, and conversely it is possible for clinical sensitivity to molds to occur in the absence of transferable reagins. For example, the serum of Case 5, Table I, contains reagins to *Alternaria*, but his symptoms could not be reproduced by nasal test with this material; on the other hand, no reagins could be demonstrated for *Aspergillus fumigatus*, although a small amount of this mold blown into his nose produced hay fever in 5 minutes.

Read before the Annual Meeting of the American Association for the Study of Allergy, New York, N. Y., June 10, 1940.
From the Allergy Dispensary, City Hospital, Cleveland.

TABLE I

MOLD ROOM TEST

GROUP A: CLINICALLY POSITIVE MOLD CASES

CASE	AGE	HISTORY	M.M. BEFORE TEST	AMT. ALT. USED	TIME EXPOSED (MIN.)	RESULT	SKIN TEST	
							S.T.	I.T.
1. J. O.	6	Summer Hf. 1 yr. Not relieved by frost Worse in humid weather	Neg.	2.5 Gm. in 1,900 cu. ft.	35	Positive; sneezing, sniffling, and running nose. Edema and pallor of M.M.	+	+ + + +
2. A. M.	33	Summer Hf. and A. 7 yr. Worse in July and August Hf. lasts until snowfall	Neg.	2.5 Gm. in 1,900 cu. ft.	65	Positive; nasal obstruction and coughing started in 3 hr. and lasted through night	0	+ +
3. T. B.	9	Summer Hf. and A. 5 yr. Worse July to December Hf. especially bad July and August Frequent A. October and November	Neg.	1 Gm. in 640 cu. ft.	30	Positive; nasal M.M. edematous, passage blocked in 20 min., coughing, sneezing, and wheezing	+ +	+ + +
4. D. L.	27	Summer Hf. 17 yr. Worse May until frost Hf. in 1938 lasted to December	Neg.	1.0 Gm. in 640 cu. ft.	50	Positive; moderate Hf. for few hours after exposure	+	+ +
5. E. S.	19	Summer Hf. 6 yr. Worse from May to December Made worse by grain, dusts, especially smutty grain	Neg.	0.7 Gm. in 640 cu. ft.	75	Negative (Positive to *Aspergillus fumigatus*)	+ +	+ + +

6. T. R.	15	Perennial Hf. and A. 12 yr. Worse in summer after exposure to grain dusts	Neg.	1.0 Gm. in 640 cu. ft.	10	Positive; A. developed in 10 min. Conjunctiva injected and watery	++	+++
7. M. O.	9	Perennial rhinitis 7 yr. "Summer colds" in June, July, and August Not relieved by frost	Neg.	0.7 Gm. in 640 cu. ft.	60	Positive; edema of mucosa, running nose, passage obstructed	±	++
8. F. G.	40	Perennial A. 20 yr. Worse April to November July and August especially bad Worse around hay dust	Neg.	1.0 Gm. in 700 cu. ft.	30	Positive; moderately severe Hf. and A. requiring adrenalin; occurred in 30 min.	+++	+++
9. R. G.	11	Summer Hf. and A. 1 yr. Hf. from July to September A. during October and November	Neg.	0.7 Gm. in 640 cu. ft.	60	Positive; edema of mucosa and moderate nasal obstruction persisting till next day	+	+++
10. M. B.	40	Perennial Hf. and A. 10 yr. Worse from June to frost Pollen therapy disappointing	Neg.	1.0 Gm. in 700 cu. ft.	30	Positive; sneezing and coughing occurred in 10 min. Tightness in chest. Wheezing after 1 hr., lasting 1 hr.		+++
11. D. S.	13	Summer Hf. and perennial A. for 9 yr. Severe Hf. from July to September Frequent attacks in November	Neg.	2 Gm. in 1,400 cu. ft.	30	Positive; tightness of chest in 30 min. Audible wheezing. Slight conjunctivitis	+	+++
12. M. W.	43	Summer Hf. one season Onset in July Did not improve until December	Neg.	2 Gm. in 1,400 cu. ft.	60	Negative	0	++

Hf., hay fever; A., asthma; M.M., mucous membrane; Alt., *Alternaria;* S.T., scratch test; I.T., intradermal test.

3. Constitutional reactions occur occasionally with mold extracts, and, although pointing toward clinical sensitivity, they are not a desirable test of clinical sensitivity.

4. The situation has been, then, that a typical mold history, a positive skin test, a transferable skin reaction, and occasional constitutional reactions indicate clinical sensitivity to molds in general. But in the individual case it still seems desirable to prove clinical sensitivity by more objective means. To this end we undertook to study our mold-reacting cases by 2 types of inhalation tests to determine if their symptoms could actually be reproduced with molds.

This paper reports the results of reproducing symptoms with the mold *Alternaria.* Similar experiments with other molds are in progress and will be reported at a later date. Patients were first tested under controlled conditions in a mold room, and subsequently nasal tests were performed with the same mold.

MOLD ROOM TEST WITH ALTERNARIA

Twenty-two patients who reacted to *Alternaria* were divided into two groups as follows: Group A, consisted of twelve patients in whom the diagnosis of clinical mold sensitivity could be made from the history itself;

Group B, 10 patients reacting to *Alternaria* in whom the diagnosis of mold allergy could not be made from the history. This grouping was done before inhalation tests were performed.

The mold room test was performed by spraying into the air of a room a quantity of killed *Alternaria* spores. The amount of mold usually averaged about 1 Gm. for every 700 cu. ft. of air. The air was kept circulating by 2 electric fans, and the rooms were prepared in the absence of the patients to avoid any suggestion. All patients were examined and found to be symptom-free before entering the room. To eliminate any element of suggestion, the attention of the patients was diverted from the actual purpose of the visit, by occupying them with such procedures as scratch tests for foods, or by giving them magazines to read or toys to play with, as the age indicated. Patients were allowed to remain in the mold room up to one hour.

Shortly after any symptoms developed, they were removed from the mold room, their noses and chests examined, and the results recorded.

Table I shows the results of mold room tests using *Alternaria* on 12 patients in Group A. All of these had a typical mold history and moderate to marked intradermal skin reaction to *Alternaria.* Eight developed symptoms of asthma or allergic rhinitis in from 10 to 60 minutes. Edema and pallor of the nasal mucous membrane with or without asthmatic wheezing were usually observed. Two additional patients developed symptoms in from 2 to 3 hours which persisted throughout the

TABLE II

MOLD ROOM TEST

GROUP B: DOUBTFUL MOLD CASES

CASE	AGE	HISTORY	M.M.	AMT. ALT. USED	TIME EXPOSED (MIN.)	RESULT	SKIN TEST	
							S.T.	I.T.
1. T. G.	13	Hf. during May and June for 5 yr. Also from Aug. 15 until frost	Neg.	2.5 Gm. in 1,900 cu. ft.	60	Negative	0	+ +
2. D. S.	6	Late summer Hf. for 3 yr. Onset usually by Aug. 1 Worse in cloudy weather	Neg.	2.5 Gm. in 1,900 cu. ft.	60	Negative	+	+ + +
3. F. V.	53	Typical ragweed Hf. for 25 yr.	Neg.	2.5 Gm. in 1,900 cu. ft.	60	Negative (slight tickling sensation in nose for ½ hr.)	0	+
4. M. S.	21	Rhinitis and eczema perennially for 6 yr. Worse Aug. 15 until January	Neg.	2.5 Gm. in 1,900 cu. ft.	60	Negative	0	+ + +
5. J. D.	45	Seasonal Hf. from Aug 15 until September	Neg.	2.0 Gm. in 1,400 cu. ft.	60	Negative	0	+ + + +
6. G. F.	5	Hf. and A. for 2 yr. during grass and ragweed season	Neg.	2.5 Gm. in 1,900 cu. ft.	60	Negative	0	+ +
7. J. P.	3	3 attacks of A., one occurring in July	Neg.	2.5 Gm. in 1,900 cu. ft.	60	Negative	0	+ + +
8. E. W.	23	Perennial eczema and A. Eczema worse during July and August	Neg.	2.0 Gm. in 1,400 cu. ft.	60	Negative	0	+ +
9. S. D.	9	Perennial nonseasonal A.	Neg.	0.7 Gm. in 640 cu. ft.	60	Negative	0	+ +
10. H. P.	13	Nonseasonal perennial A. for 10 yr.	Neg.	2.5 Gm. in 1,900 cu. ft.	60	Positive; moderate wheezing and coughing lasting ½ hour	0	+ + +

Controls: Four normal, negative; three allergic, negative.

For explanation of abbreviations, see footnote to Table I.

night. Of the 2 nonreactors, Case 5, E. S., had negative results with *Alternaria* but markedly a positive nasal test with *Aspergillus fumigatus* and with grain smuts.

Table II shows the results of exposing 10 patients in Group B (doubtful mold cases) to same amounts of powdered *Alternaria* under the same circumstances for one hour in a mold room. All were moderately strong reactors to *Alternaria* intradermally, but nothing in the history suggested mold allergy. Five of these patients were typical pollen hay fever cases (Cases 1, 2, 3, 5, and 6), as seen by their histories. The remaining cases were patients with perennial hay fever or asthma, most of whom were worse during at least part of the summer. Of these ten patients, only one, Case 10, developed symptoms after one hour of exposure.

TABLE III

NASAL TEST WITH ALTERNARIA

GROUP A: CLINICAL MOLD CASES

CASE	AGE	MUCOUS MEMBRANE BEFORE TEST	TIME OF EXPOSURE (MIN.)	RESULT	MOLD ROOM TEST
1. J. O.	6	Negative	30	Positive; edema and pallor of mucous membrane	Pos.
2. A. M.	33	Negative	40	Positive; edema and pallor of mucous membrane. Sneezing and coughing in 15 min.	Pos.
3. T. B.	9	Negative	10	Positive; very marked edema and pallor of mucosa; absolute occlusion of passage	Pos.
4. D. L.	27	Negative	30	Positive; slight edema of mucous membrane. No sneezing. Itching sensation; running nose	Pos.
5. E. S.	19	Negative	5	Negative (very positive with *Aspergillus fumigatus*)	Neg.
6. T. R.	15	Negative	15	Positive; wheezing in 15 min.	Pos.
7. M. O.	9	Negative	30	Positive; sneezing after 10 min. Coughing after 15 min. Some edema of mucous membrane and slight pallor. Hay fever all night and next morning	Pos.
8. F. G.	40	Negative	15	Positive; sneezing in 5 min. In 15 min. mucous membrane was moderately edematous and obstructed; moderately severe asthmatic wheezing occurred, requiring adrenalin	Pos.
9. R. G.	11	Negative	15	Positive; mucous membrane became edematous and pale. Closure of passage, marked sneezing and running nose	Pos.
10. M. B.	40	Negative	10	Positive; mucous membrane slightly edematous and definitely pale; moderate nasal obstruction; moderately severe asthmatic wheezing and coughing in 10 min.	Pos.
11. D. S.	13	Negative	40	Positive; some sneezing and nasal obstruction; swelling of turbinate; no asthma	Pos.
12. M. W.	43	Negative	30	Negative	Neg.

After inhalation tests were completed, the scratch tests were then performed, with the interesting result that only one positive scratch test to *Alternaria* was obtained in this group. Four normal controls and 3 allergic control patients developed no symptoms after one hour in the mold room.

A positive mold room test probably indicates true clinical sensitivity. But this method has certain obvious disadvantages, chief of which is the use of large quantities of powdered mold. Over 15 Gm. of *Alternaria* were used in this present study.

A nasal test with molds, if nonirritating, would have great advantage by virtue of simplicity as a practical test for clinical allergy to molds. Powdered *Alternaria*, therefore, was blown into the patients' noses, at first with a powder blower, and more recently by a simpler method. A small quantity of powdered mold is held on a flat toothpick before the nostril and the patient is asked to breathe deeply. The powder is easily inhaled into the respiratory passage.

Table III shows the results of nasal tests with *Alternaria* in 12 patients in Group A (clinically positive mold cases) who had been subjected previously to the mold room test. Ten of these patients gave a positive nasal test in from 10 to 40 minutes. This usually consisted of sneezing, coughing, or wheezing, and the nasal mucous membrane became edematous and pale, with the air passage often occluded. Two patients required adrenalin for relief of asthma. In several cases the symptoms

TABLE IV

NASAL TEST WITH ALTERNARIA

GROUP B: DOUBTFUL MOLD CASES

CASE	AGE	MUCOUS MEMBRANE BEFORE TEST	TIME OF EXPOSURE (MIN.)	RESULT	MOLD ROOM TEST
1. T. G.	13	Negative	30	Negative	Neg.
2. D. S.	6	Negative	35	Positive; moderate edema and pallor of mucous membrane. Sneezing and coughing after 10 min.	Neg.
3. F. V.	53	Negative	35	Negative	Neg.
4. M. S.	21	Negative	30	Negative	Neg.
5. J. D.	45	Negative	70	Negative	Neg.
6. G. F.	5	Negative	60	Negative	Neg.
7. J. P.	3	Negative	30	Negative	Neg.
8. E. W.	23				Neg.
9. S. D.	9	Negative	20	Negative	Neg.
10. H. P.	13	Negative	60	Negative	Pos.
11. G. L.	52	Negative	60	Negative	
12. D. A.	19	Negative	15	Doubtful; slight swelling at point of application. Developed rhinitis in few hours	
13. F. W.	30	Negative	20	Negative	
14. L. F.	17	Negative	30	Negative	
15. W. V.	10	Negative	30	Negative	
16. F. W.	38	Negative	30	Negative	
17. J. P.	11	Negative	60	Negative	
18. I. F.	15	Negative	60	Negative	

persisted one or more days. The result of the mold room test is repeated in Table III for comparison. The results of both tests were identical in each of the 12 cases.

Table IV shows the results of blowing powdered *Alternaria* in nine patients in Group B (doubtful mold cases). One patient, Case 2, developed sneezing and coughing, with edema and pallor of the nasal mucosa, within 10 minutes. All other results were negative. The results of the mold room test are repeated for comparison, and 2 discrepancies are noted in these 10 doubtful mold cases. In addition, the nasal test was tried on 8 patients reacting to *Alternaria* who were not tested in the mold room. These were all classed as doubtful since their histories did not suggest mold allergy. One of these patients gave a questionable reaction to the *Alternaria* nasal test.

SUMMARY

1. In an effort to evaluate clinical mold sensitivity, 22 patients reacting to *Alternaria* were subjected to a mold room test with powdered *Alternaria*. Half of them developed hay fever or asthma (Table V).

TABLE V

RESULTS OF INHALATION TESTS WITH ALTERNARIA

		NO TESTED	RESULTS	
			POSITIVE	NEGATIVE
	1. Mold Room Test			
Group A:	Clinically positive mold cases	12	10	2
Group B:	Doubtful mold cases	10	1	9
	Total	22	11	11
	2. Nasal Test			
Group A:	Clinically positive mold cases	12	10	2
Group B:	Doubtful mold cases	9	1	8
	Other doubtful mold cases	8	1?	7
	Total	29	11 and 1?	17

2. Ten of 12 patients whose histories suggested mold allergy gave a positive mold room test, while only one of 10 doubtful mold cases developed a positive mold room test with *Alternaria*.

3. When powdered *Alternaria* was blown directly into the noses of patients reacting to *Alternaria*, 10 of 12 clinically positive mold cases reacted, but only one positive and one questionable positive reaction were obtained of 17 so-called doubtful mold cases.

4. A typical mold history probably indicates true clinical mold sensitivity in the presence of a positive scratch test.

5. The nasal test with *Alternaria* is simple, and if done outside the mold season, is a safe and reliable means of evaluating *Alternaria* sensitivity.

6. An interesting parallel between a positive scratch test to *Alternaria* and inhalation tests by either the nasal or mold room method is noted.

7. These experiments demonstrate the importance of *Alternaria* as an allergen.

REFERENCE

1. Feinberg, S. M.: Seasonal Hay Fever and Asthma Due to Molds, J. A. M. A. 107: 1861, 1936.

DISCUSSION

DR. MILTON B. COHEN, Cleveland.—I think Dr. Harris is to be commended for this very excellent study. When I first contacted him several years ago, he told me that a great many people reacted to *Alternaria* and that he was convinced there was a great deal of mold sensitivity. I said that I would like to be convinced. Many of my patients react, but I do not always know whether or not they are clinically sensitive. I wish we had some method other than an immunologic one that might tell us something about the actual importance of these histories and of the skin tests which we get.

It seems to me that this presentation—and I am certain it has been carried out as Dr. Harris says, because I know the care with which he does his work—demonstrates conclusively that the mold *Alternaria* can produce active symptoms and that it is of relatively more importance than some of us have thought on the basis of our experience.

DR. HARRY S. BERNTON, Washington.—At this time, no one questions the fact that *Alternaria* is capable of producing symptoms of asthma. One feature of the experiment is noteworthy, namely, that spores have been blown into a room and the air kept in circulation by electric fans. It has been recognized by some investigators that any chilling of the body surface will either provoke or aggravate symptoms of hay fever or asthma. The question naturally presents itself whether the symptoms in the patients have resulted from the chilling of the body surface or from exposure to the molds.

DR. GEORGE BLUMSTEIN, Philadelphia.—For many years we have been using the nasal test, not only for detection of mold sensitivity, but also for the detection of pollen sensitivity. Our experience with this test has led us to the conclusion that it is an invaluable objective clinical test that is most often in agreement with the clinical history. There are a few things, however, that vary when this test is applied to mold-sensitive patients as contrasted with pollen-sensitive patients. Several of our mold-sensitive patients who gave negative skin reactions have given positive nasal tests to the powdered mold extracts. There has been no consistency in these reactions that might lead one to believe that we were dealing with common antigenic factors. Many of these patients showing positive nasal tests and negative skin tests failed to manifest clinical symptoms even when the atmospheric concentration of the mold was greatest. The explanation for this evident paradox is as yet unknown, but we are attempting to solve it and hope to report on this phase of the problem at a later date.

Another difference between the mold and pollen patients lies in the preponderance of bronchial symptoms (e.g., cough and wheezing) and the lack of eye symptoms in the former, as contrasted to the prominence of eye signs and paucity of bronchial symptoms in the latter.

Several of our patients clinically sensitive to mold exhibited negative eye and positive nasal tests. This has invariably been in agreement with their histories, wherein eye signs were generally lacking. Pollen-sensitive patients, on the other hand, never show a positive nasal test without a positive skin and eye test.

DR. ROBERT CHOBOT, New York.—We reviewed this question of mold sensitivity, particularly *Alternaria* sensitivity, from the standpoint of the serologic changes of skin sensitivity, and of eye tests, environmental tests, and insufflation. Our paper is to be published. Briefly, results are these:

Of 240 cases, sixty-six (27.5 per cent) gave positive skin reactions to *Alternaria*. Twelve patients of a series of twenty-eight selected ones with positive skin reactions in both children and adults were found to be sensitive. Eye tests were positive when passive transfer and insufflation were positive. Eye testing is an easy check on the need for therapy. Plates exposed in their homes showed seven of twenty-eight patients having molds to which they were skin sensitive.

Insufflation tests in the sense of opening a Petri dish of pure ordinary culture and allowing a patient to inhale it, to our great surprise, produced nothing. If, however, we took a swab or an applicator covered with *Alternaria* and carefully put it on the turbinate or blew ordinary spores in a goodly quantity into the nose, some surprising findings occurred. The result was this: About 12.5 per cent of inhalant-sensitive cases were definitely sensitive to *Alternaria* mold. When I say sensitive, I mean skin sensitive, serologically sensitive, eye sensitive, and insufflation sensitive.

In addition, we took the trouble to neutralize sera to mold extracts, and found that serologically these things are specific, they neutralize specifically, and when a serum that is sensitive to ragweed and timothy and, say, *Alternaria,* neutralizes to ragweed, it will neutralize to timothy and the *Alternaria* remains untouched, or *Alternaria* can be knocked out and timothy and ragweed remain untouched. In other words, there is a specific immunologic type of sensitivity which differs in no sense from pollen in our experience, in which one can demonstrate positive eye tests, nose tests, skin tests, and serologic tests. We have found a short cut to the serologic study by doing eye tests because we have yet to see a patient who had a positive insufflation test who had a negative eye or a negative passive transfer.

So that if one gets a positive mold reaction and takes the trouble to use extracts standardized on a protein nitrogen basis, and if he uses them as an eye test in rather strong solutions, certainly no less than 5,000 units for an eye test, one will find a lot of these mold reactions that have puzzled us so greatly sorting themselves out and having a great deal of real meaning.

DR. SAMUEL M. FEINBERG, Chicago.—I want to commend Dr. Harris' work, which is very exact. While we have not published anything like this on a systematic basis, we have, from the beginning, done some of this work on inhalation in our original clinical experiments. I want to agree with Dr. Chobot in everything he has said, including the efficacy of the conjunctival tests.

If I may review Table V again I think it pays to emphasize something Dr. Harris has mentioned, namely, one can make a diagnosis by the clinical history even better than by the inhalation tests.

As a matter of fact, twelve patients were clinically sensitive and fifteen had positive inhalation tests. These had clinical stories that agreed actually with symptoms, and I presume that they subsequently proved to be clinically mold-sensitive. In other words, the clinical story itself would be probably sufficient; if you combine the clinical story with the ordinary scratch test, it is almost 100 per cent positive. Dr. Harris, of course, has given us additional evidence, but I will say definitely that ordinarily for diagnosis you rarely need the inhalation test, any more than you need it for a ragweed pollen patient who says he has hay fever from the middle of August to frost. Certainly, we are satisfied with a simple scratch test ordinarily because it agrees so well with the clinical diagnosis.

Dr. George L. Waldbott, Detroit.—I should like to ask Dr. Harris why he prefers the scratch test to the intradermal test. If I interpret his tables correctly, there was a definite parallelism between both tests, with the difference, however, that the intradermal test was more sensitive.

Dr. Charles N. Hensel, St. Paul.—Before concluding the discussion, I would like to have the writer tell us what are the necessary criteria for a typical mold history.

Dr. Harris.—Dr. Bernton comments about the chilling of the body surface. This factor of chilling, of course, may have some influence, but I do believe that it was of equal influence in both of the groups.

Dr. Chobot's remarks regarding neutralization with *Alternaria* were of particular interest. We have done some similar work and were able to show that, while *Alternaria* is a very common contaminant in various grains, cross neutralization could not be shown to exist between the antigen of *Alternaria* and the antigen of wheat dust and oat dust.

Dr. Waldbott asked why we preferred the scratch test to the intradermal test. If this small series can be used as a reliable criterion, then I believe that the intradermal test was only 50 per cent reliable, and that was what we were trying to evaluate, namely, whether or not the intradermal test was a reliable test. My feeling is that it is definitely not, whereas the scratch test gives a very close correlation with the history.

The last question concerned a typical mold history. I intentionally omitted that in order to save time.

SENSITIVITY TO GUM ACACIA, WITH A REPORT OF TEN CASES OF ASTHMA IN PRINTERS

C. B. Bohner, M.D., Indianapolis, Ind., and J. M. Sheldon, M.D., and J. W. Trenis, M.D., Ann Arbor, Mich.

ISOLATED reports of sensitivity to acacia (gum arabic) have appeared in medical literature. We wish to review these, to discuss the chemistry and physiologic action of acacia, and to report ten cases of asthma caused in printers by this material.

Spielman and Baldwin[1] in 1933 presented a case they believed to be the first of proved sensitivity to gum arabic. The patient worked in a candy factory. Levin[2] reported one case in a printer, and Marsh[3] has recently reported three cases of acacia sensitization that he observed, all in printers. Maytum and Magath[4] reported nasal obstruction, lacrimation, difficulty in breathing, cough, loss of voice, and a suggestion of laryngeal stridor in a 27-year-old girl a few minutes after the injection of this gum. These observers considered the reaction anaphylactoid. They emphasized that it was the first allergic reaction in over 3,000 acacia infusions given at the Mayo Clinic. It is interesting to note that the patient had received a similar infusion seven months earlier. The authors comment that acacia is given for shock and a second infusion to the same patient is quite rare.

Studdiford[5] has reported severe and fatal reactions following intravenous use of acacia-glucose infusions. In all of his patients, the reaction consisted of cyanosis, dyspnea, tachycardia, edema of the lungs, and a sense of impending death. Several of these reactions occurred shortly after obtaining a new pharmaceutic supply of the drug. The author was particularly impressed with the autopsy findings of liver damage. He also attributed part of the reaction to poor absorption of gases caused by the gum which coated the red blood cells, as Christie and co-workers[6] have demonstrated. It has been the opinion of some workers that the reactions were caused by a poorly prepared acacia solution.[5, 7]

Chemically, acacia is classed as an inert colloid. It is considered to be a polysaccharide member of the carbohydrate family, related polysaccharides being glycogen, dextrin, cellulose, and starch. All are amorphous, odorless, and translucent, and on hydrolysis yield one or more sugars, usually pentoses and hexoses.

Uhlenhuth and Remy[8] found 0.3 per cent of nitrogen present in samples of purified gum acacia. Spielman and Baldwin[1] found 0.5 per cent of total nitrogen in an analysis of this material and noted a positive biuret test indicating the presence of protein nitrogen. In an

From the Indiana University Medical School, Indianapolis, and the Medical Department, University of Michigan, Ann Arbor.

analysis of three samples purchased on the open market, we have found an average of 0.48 per cent of nitrogen and a positive biuret test.

Uhlenhuth and Remy[8] have demonstrated the presence of precipitins and complement-fixing antibodies in rabbits injected with purified acacia. No such reactions were produced when starch, dextrin, gelatin, tragacanth, gum cherry, or gum gutta was used.

Maytum and Magath[4] injected nineteen guinea pigs intraperitoneally with acacia and four weeks later gave them an intravenous injection of the same material. In seven there was no anaphylactoid reaction; in four the reaction was mild; in three, fairly severe; in two, severe; and in three, fatal. They concluded that this gum had antigenic properties.

Spielman and Baldwin[1] tested thirty routine patients for gum arabic sensitivity by scratch and intradermal methods and found no positive reactions. These authors quote the findings of Farrar in patients receiving intravenous infusion of acacia, with negative skin tests ten to twenty-five days after infusion.

Acacia has many uses, among which are the following:

Commercial

Shoe polish manufacture
Water colors, transparent
Metal polish manufacture
Various paints
Many varnishes
Linoleum
Oil cloth
Match heads
Printing textiles
Porcelain
Ceramics
Spray for paper sizing
Textile fibers
Fireworks
Mucilage
Glues
Cements
Adhesive pastes
Confections
Sweetmeats
Bakery products
Process engraving
Potteries
Stiffening
Luster for crepe silk
For body and drier in writing and lithograph inks

Medical

Mucilage of acacia
Vehicle and pill excipient
Emulsifier

The cases of asthma studied were in printers who were sensitive to the acacia used in "offset spray." This spray is being employed more frequently because of the use of colored ink in an increasing number of publications. As each sheet is printed, the spray comes in contact with it, and this forms a fine film over the freshly colored sheet, thus preventing "offset" or smearing of the colored matter onto the next sheet added to the stack. With the spray machines used for this work, a coating of the solution has been noted on workmen's glasses 20 feet from the machine. With proper lighting, one may see a mist spreading well beyond the printing press.

CASE REPORTS

CASE 1.—P. A., white male, married, aged 53 years, a printer for eleven years, was first seen on Feb. 18, 1938, at which time he complained of asthma and severe coughing attacks. He had developed influenza in December, 1937; this was fol-

lowed by some tightness in his chest. He had no fever or cough. He was able to continue his work, but he gradually developed breathlessness during the next three months and had two severe attacks of asthma which were relieved by the administration of epinephrine hydrochloride. He had noticed that he was more dyspneic while at work. He had no other allergic manifestations, and there was no family history of allergic diseases. Except for an attack of lumbago six or eight years before, he had always been in good health.

This patient was a well-developed, well-nourished, adult male. The blood pressure was 122/80; the pulse rate varied from 86 to 90, with occasional extrasystoles. The heart sounds were normal, and there was no cardiac enlargement. The chest was emphysematous, with dry asthmatic râles audible throughout the lung fields. The remainder of the physical examination was negative.

Cutaneous tests with 150 inhalant, pollen, and food allergens were negative. Nasal smears were negative, as were blood and urine examinations. Stained sputum smears showed from 16 per cent to 24 per cent eosinophilic staining cells. Stereoscopic roentgenograms of the chest showed a normal-sized heart with a thickening of the basilar trunk markings. X-ray examination of the accessory nasal sinuses revealed evidence of chronic infection.

The patient was again seen on Sept. 26, 1938, at the Long Hospital of the Indiana University Medical Center. During the intervening seven months the usual measures had been carried out to determine the cause of his asthma, and various drugs, including digitalis, had been given. There had been no lessening of symptoms. Physical examination on this admission was essentially the same as previously observed except for a low-grade paranasal sinusitis and 18 pounds weight loss.

Repeat cutaneous and intracutaneous allergic tests were negative except for a four-plus reaction to gum arabic. (A second printer with asthma had been found sensitive to offset spray in March, 1938.) The history then revealed that an "offset spray" had been installed at his place of work in June, 1937, six months before the onset of his asthma.

The patient was advised to change his occupation. He refused to comply with this request and continued to show symptoms until a dextrose base solution was substituted for the acacia material in the offset spray. Subsequent examination revealed freedom from symptoms.

CASE 2.—H. D., white male, aged 29 years, was admitted to the University of Michigan Hospital on May 27, 1938, complaining of difficulty in breathing of three months' duration. In February, 1938, two weeks after beginning work in a printing establishment, he noted difficulty in breathing, associated with wheezing. His work was that of spraying a "drying material" on printed matter in the plant. Several other workers had some "cough and congestion in the morning," but he knew of no cases with complaints as severe as his own. There was no history of previous allergic manifestations. One sister suffered with hay fever.

The physical examination on his first visit was not contributory. Four days later he was seen again, and examination showed the skin to be warm and flushed and the temperature to be 99° F. There were sibilant and sonorous râles over the lung fields.

Examination of the blood showed no eosinophilia. A nasal smear was likewise negative. Stereoscopic x-ray examinations of the chest showed no definite abnormalities. Cutaneous and intracutaneous testing disclosed moderate reactions to June grass, orchard grass, timothy, and short ragweed, rather marked reactions to stock house dust, and a good reaction to gum acacia.

In view of the history which suggested that the spray might be a possible cause of his symptoms, a cutaneous test was made with "drying spray," with a resultant marked reaction. On June 14, 1938, he was placed in a small room

which was then sprayed with a solution of alcohol, ether, and gum acacia. Following a fifteen-minute exposure in the room he developed typical allergic conjunctivitis and rhinorrhea and a sensation of nasal obstruction with objective evidence of an allergic rhinitis. The following day the above procedure was repeated, with development of typical allergic conjunctivitis, allergic rhinitis, and mild asthma. The patient's symptoms promptly disappeared upon change of occupation.

Eight other cases of sensitivity to acacia have been observed. All patients worked in printing plants. Two of them were women.

Acacia seems to be a highly specific allergen. All ten patients gave strongly positive direct tests to this material, and the sera of three gave positive transfer tests. Passive transfer tests were not made on the other seven patients. The direct transfer tests were negative to Indian gum and tragacanth. Sixteen highly allergic patients and ten normal controls all gave negative reactions to gum arabic. One of us (C. B. B.) has tested routinely with it for the past eighteen months. Results have been negative.

SUMMARY

1. A group of ten patients in whom direct exposure to acacia initiated severe asthmatic seizures have been studied. All were exposed to this material by offset sprays used in the printing industry.

2. Apparently acacia (gum arabic) is an industrial hazard, and sensitization to it is not rare. It is suggested that dextrose be substituted for acacia in offset sprays.

3. The time of gross exposure to this spray material before the onset of asthmatic symptoms varied from two weeks to twelve months.

4. Eight of the ten patients were adult males ranging in age from 22 to 53 years. This high incidence of males may be explained by the fact that relatively few females are employed in the printing industry.

5. The increasing use of gum arabic in the printing of magazines, box labeling, and other industrial sources presents the possibility of more widespread allergy to acacia.

REFERENCES

1. Spielman, A. D., and Baldwin, H. S.: Atopy to Acacia (Gum Arabic), J. A. M. A. **101**: 444, 1933.
2. Levin, S. M.: The Importance of Careful Environmental Studies in Allergic Patients, J. Michigan M. Soc. **38**: 486, 1939.
3. Marsh, C. D.: Personal communication.
4. Maytum, C. K., and Magath, T. B.: Sensitivity to Acacia, J. A. M. A. **99**: 2251, 1932.
5. Studdiford, W. E.: Severe and Fatal Reactions Following Intravenous Use of Gum Acacia Glucose Infusions, Surg., Gynec. & Obst. **64**: 772, 1937.
6. Christie, A., Phatax, N. M., and Olney, M. B.: Effect of Intravenous Acacia on Physio-Chemical Properties of Blood, Proc. Soc. Exper. Biol. & Med. **32**: 670, 1935.
7. Cotin, Schrift, M. H., and Ruggiero, W. F.: Production of Pyrogen in Gum Acacia by Bacteria, Proc. Soc. Exper. Biol. & Med. **41**: 533, 1939.
8. Uhlenhuth, P., and Remy, E.: Zur Frage der Antikörper gegen Kohlenhydrate (Gummi Arabicum), Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**: 318, 1933; also Klin. Wchnschr. **12**: 911, 1933.

DISCUSSION

DR. SAMUEL H. HURWITZ, San Francisco.—In 1916, Dr. George H. Whipple carried out a series of experiments, in which I was associated, in an attempt to produce marked secondary hemorrhages. These studies led to the discovery of the antianemic substances in liver. We found that by plasmapheresis, that is, the removal of the red corpuscles and the replacement of the blood volume with a mixture of 6 per cent acacia (gum arabic) in saline solution, we could preserve the life of those animals for a longer period of time without having them die as a result of tremendous drop in the blood pressure. We did not understand the importance of the gum as a potent factor in the production of acute anaphylactic shock at that time. But some of the animals, after an incubation period and a subsequent infusion of acacia in saline, died in acute anaphylactic shock. The pathologic studies carried out by Dr. Whipple showed the typical classical lesions of anaphylactic shock in dogs. There were lesions in the liver, chiefly necrosis, and also hemorrhagic edema of the mucous membranes high in the small intestine.

Despite supplemental studies, some of us used infusions of acacia in saline in man in case of surgical shock at the time, because twenty-four years ago we did not have available the ready method of transfusion and the preserved bloods which we have at the present time. Despite the use of the infusions of acacia in saline in man in surgical shock, which were subsequently used very extensively in the World War, we heard very little about the clinical effects of infusions of acacia in saline. About 1922, we began to see reports in the literature concerning its untoward effects. But despite the thousands of cases in which such infusions have been used, we heard very little about the allergic manifestations to which Dr. Bohner called our attention.

Of course, it is very easy to understand. In the first place, as Dr. Bohner stated, these patients received one infusion of saline and acacia, rarely received the second, and, if they did receive the second, it was at a considerable interval after the first. Probably also because of the rapid elimination of the acacia in the urine, we may not have seen these marked clinical manifestations of allergy following infusions of acacia in saline.

The method of absorption in the spray, however, is quite a different thing. There one is dealing with repeated exposures and slow absorption of acacia by the membranes of human beings.

DR. SHELDON.—We do not wish to enter any argument for or against the use of acacia infusions, but we do wish to emphasize the possibility of severe allergic reactions occurring from indiscriminate use of acacia for intravenous infusions.

GENERALIZED ALLERGIC REACTIONS TO INSULIN

Review of the Literature, With Report of a Case

Elton Yasuna, M.D.
Boston, Mass.

SINCE the introduction of insulin by Banting and Best in 1922, the literature has contained reports of allergy to this substance. In recent years insulin in its crystalline form has been isolated and analysis has shown it to be a protein.[1] Therefore, because of its protein nature, insulin allergy will always be a problem which must be faced when the occasion arises.

It has been claimed by Herold[2] that the incidence of tuberculosis and diabetes in allergic persons is very low. Joslin[3] states, however, that "associated diseases, notably allergy, tuberculosis and epilepsy are prone to occur in diabetes." Also, Joslin continues, "Allergy has been demonstrated by Kern[4] to recur frequently in diabetic families."

Chemical studies by Abel[5, 6] and others have shown that insulin prepared from either beef or pork pancreas contains an average of from 0.006 to 0.01 mg. of nitrogen per unit even after purification and recrystallization. Abel concludes that "this amount of protein is so small that in the average case the possibility of inducing generalized hypersensitivity by repeated administration is unlikely, and reports in the literature consequently are rare."

Insulin allergy may be an allergy to the insulin factor itself, or it may be due to the pancreatic tissue of the animal, an impurity contained in commercial insulin. To eliminate the possibility of sensitivity being due to the pancreatic tissue impurity, Altshuler[1] and others have suggested a trial test with crystalline insulin; if the patient shows a disappearance of allergic symptoms, one is justified in concluding that the sensitivity is due to the animal impurity in the commercial preparations rather than to the actual insulin itself. Also, skin testing with the various insulin preparations has been found reliable and may be used to detect the antigen which is precipitating allergy. Lewis[8] has found the majority of cases to be sensitive to the insulin protein itself rather than to the animal tissue. Recently, the introduction of protamine insulin by Hagedorn[9] has added a new source of allergy, i.e., the protamine factor which is of a protein nature. In these instances a comparison of the action of regular insulin with that of protamine will show readily whether sensitivity is due to protamine.

From the Fifth Medical Service, (Boston University), of the Boston City Hospital, and the Diabetic Clinic of the Boston City Hospital.

Allen[10] and Scherer have inquired, if crystalline insulin as isolated today is the same as human insulin, how the body can be sensitive to a substance identical to something within itself. Two explanations offered conclude that either crystalline insulin as we know it today varies from human insulin, or it is not a pure substance. The belief of some investigators that insulin is not a pure hormone, but a mixture of substances, is disputed by Abel who, in a personal communication to Davidson,[11] wrote, "In different species of animals the various insulins all have the same composition and crystalline form, but differ in respect to the interior arrangement of their component amino acids, and it is on this, just as in the case with various proteins from different animals, that the difference in allergic response rests." However, in the state of our present knowledge we must accept crystalline insulin as a complete and soluble protein with antigenic qualities. This has been amply demonstrated by Lewis[8] and by Bernstein and coworkers[12] who have produced anaphylaxis in guinea pigs with crystalline insulin after previous sensitization.

Case reports have appeared in which a sensitivity to insulin is claimed, as manifested by a severe fall in blood sugar levels after small doses, with consequent difficulty in controlling the diabetes. Stotter[18] observed that one of his patients had hypoglycemic reactions following the administration of small amounts of insulin. He found that this patient had positive skin test reactions to insulin, and he proceeded to desensitize the patient. The hypoglycemic reactions ceased, the skin test to insulin became negative, and the diabetic state was well controlled. It is possible that this type of case represents a sensitivity to insulin not as a protein matter but as a hormone with an exaggerated physiologic response; whereas the insulin allergy under discussion in this paper is a sensitivity to insulin as a protein, with resulting urticaria, vasomotor collapse, etc.

The incidence of allergic response to insulin merits a brief consideration. Lawrence,[19] in England, reported in 1925 that 30 per cent of his cases showed some sensitivity to insulin, consisting entirely of reactions localized to the site of injection; Joslin, as quoted by Rackemann[20] in 1931, gave his incidence as between 10 and 20 per cent. Allen and Scherer,[13] in their review of cases at the Mayo Clinic during the ten years from 1922 to 1932, found that from 8 to 12 per cent of patients using insulin showed some sensitivity to it. Collens and associates,[21] in a small series of cases, reported an incidence of 7.3 per cent. These figures appear to be rather high when compared with the general impression gained in diabetic clinic work, but probably many patients in the clinic will not offer information on local reactions unless specifically asked. A review of the 3,323 diabetic admissions*

*This figure represents diabetic admissions and not diabetic patients. One diabetic patient may have several admissions.

to the Boston City Hospital since 1921 (the year insulin was introduced) failed to reveal a case of generalized insulin sensitivity. One woman, a 63-year-old diabetic patient, was admitted for a diarrhea which ceased on discontinuation of insulin, but no skin tests or further studies were recorded. Several patients showed local insulin reactions in the form of urticaria and erythema. However, it was not possible to determine accurate percentage figures on patients showing local reactions to insulin since no notation on this subject was made in many of the cases.

Of the cases sensitive to insulin, Allen and Scherer[13] estimate that from 98 to 99 per cent will show a reaction limited to the site of injection, while only from 1 to 2 per cent will exhibit general or systemic manifestations. Thus, it is estimated roughly that only one person in one thousand using insulin will show a systemic reaction.

Allen and Scherer[13] have divided the cases of insulin allergy into three groups:

1. Mild Local Reaction at the Site of Injection.—This group manifests itself by a stinging or smarting sensation at the site of injection, followed by an area of redness and induration. The maximum reaction occurs in from twelve to twenty-four hours after injection and usually subsides in from one to three days. This type of reaction must not be confused with local irritation due to alcohol on the needle. The alcohol irritation occurs within a few minutes from the time of injection and subsides within an hour. Allen and Scherer estimate that about 85 per cent of patients allergic to insulin are included within this first group.

2. Severe Local Reaction at the Site of Injection.—This group exhibits the same symptoms and signs as in the first group, but in a more severe form. Severe pain at the site of injection is experienced frequently and is followed by marked induration. A localized area of urticaria and erythema may be present. After months or years of treatment, the patient may have many areas of induration at the sites of injection. This group constitutes about 10 to 15 per cent of the total number of patients sensitive to insulin.

3. General or Systemic Reactions.—This small group represents only 1 per cent of the patients sensitive to insulin. The allergic response may be manifested by cutaneous, circulatory, and gastrointestinal symptoms.

The cutaneous reactions are in the form of urticaria, edema, numbness, tingling, and itching. One or all of these manifestations can occur and may be generalized or limited to certain areas. Most cases of generalized allergic reactions to insulin show skin signs and symptoms.

The circulatory reactions are those of pallor, flushing, palpitation, fall in blood pressure, weak pulse, and circulatory collapse. Circulatory symptoms are seen frequently and may be very severe.

Finally, gastrointestinal complaints such as nausea, vomiting, abdominal cramps, and diarrhea have been reported following insulin therapy in patients allergic to the medication. These are uncommon but may be encountered occasionally.

It is undecided whether lipo-atrophy following insulin injection is a sensitivity to insulin or whether it is a simple fat necrosis due to irritation. Although debatable, these cases are included under insulin sensitivity for the present. This group shows an atrophy of subcutaneous fat at the site of injection, resulting in a depression of the skin. This lipo-atrophy is usually a delayed occurrence, sometimes not appearing until a few years after the beginning of injections. It is comparatively rare, only a handful of cases having been reported in the literature to date.[14-17]

In the early period of insulin therapy before adequate methods of purification and concentration were known, hypersensitivity reactions were reported not infrequently. In all instances, reactions followed the injection of from 5 to 15 c.c. of the early unpurified insulin containing relatively large amounts of protein. Reactions were usually in the form of a mild serum sickness.* An exception was found in the case of Raymond and La Croix,[29] in which sensitivity occurred on the fifty-fifth day of insulin therapy and consisted of generalized urticaria, constriction of the chest, edema of the face, pruritus, and vasomotor collapse.

By 1925 the concentration and purification of insulin preparations[5, 6] had reached a point where the total amount of protein in therapeutic doses was not sufficient to cause a foreign protein or "serum" reaction. Tuft, Allen, and other workers in the field of insulin allergy claimed that cases of generalized insulin sensitivity reported before 1926 could not be accredited to insulin because the reactions were of the nature of serum sickness and also because skin testing with insulin had not been done. From 1926 thereafter, commercial insulin was highly purified and case reports were more reliable. Although I have mentioned the cases reported in the literature prior to 1926, these have not been included in the final tabulation (Table I) since they represent reactions to large amounts of foreign protein and not to insulin itself.

A review of the literature since 1926 reveals eleven cases in which generalized sensitivity was definitely shown by means of skin tests

*Thus in 1922 twelve cases of generalized reactions to insulin were reported in the American literature by Williams (two cases),[22] Wilder (three cases),[23] Joslin (four cases),[24] and Geyelin (three cases);[25] single cases were reported abroad in 1924 by Lereboullet,[26] Mauriac,[27] and Umber.[28] In 1925, Raymond and La Croix[29] and Achard and Bloch[30] each reported a case.

TABLE I

PROVED CASES OF GENERALIZED SENSITIVITY TO INSULIN WHICH HAVE APPEARED IN THE LITERATURE

AUTHOR	AGE, SEX	HISTORY OF ALLERGY	SKIN TEST RESULT	SYMPTOMS	NUMBER OF INJECTIONS BEFORE ALLERGY	THERAPY	HISTORY OF LAPSE OF THERAPY
Tuft (1938)	62, F	No	Insulin and crystalline positive	Nausea, vomiting, edema, urticaria, pruritis, prostration	18	Insulin discontinued	Yes
Allen and Sherer (1932)	48, F	Yes	Insulin and crystalline positive	Prostration, urticaria, dyspnea	4	Insulin discontinued	Yes
Allen and Sherer (1932)	46, M	Unknown	Insulin and crystalline positive	Urticaria, redness, burning	6	Insulin discontinued	No
Allen and Sherer (1932)	40, F	Yes	Insulin positive; crystalline unknown	Urticaria, pruritus	10	Insulin discontinued	No
Allen and Sherer (1932)	50, F	Yes	Insulin positive; crystalline unknown	Urticaria of knees, hands, and neck	5	Insulin discontinued	Yes
Bryce (1933)	F	Unknown	Insulin positive; crystalline unknown	Urticaria, pruritus	Unknown	Desensitized	Unknown
Davidson (1934)	62, F	No	Insulin and crystalline positive	Urticaria, pruritus, eruption	15	Insulin discontinued; patient lost	Yes
Sammis (1935)	F	Yes	Insulin and crystalline positive	Urticaria	1	Insulin discontinued	No
Corcoran (1938)	56, F	Yes	Insulin and crystalline positive	Urticaria	11	Desensitized	Yes
Herold (1938)	23, M	Yes	Insulin and crystalline positive	Urticaria, edema, pruritus, dyspnea	12	Desensitized	No
Ulrich, Hooker, and Smith (1939)	53, M	Yes	Insulin and crystalline positive	Urticaria, constriction of chest	9	Desensitization unsuccessful	Yes
Yasuna (1939)	43, F	Yes	Insulin and crystalline positive	Urticaria, constriction of chest, edema	4	Insulin discontinued	Yes

with commercial and crystalline insulin preparations to be due to the insulin factor. These cases are tabulated in Table I. Ten were reported in the American literature. In addition twelve cases* were described in which a generalized allergic response occurred following the injection of insulin, but in which allergy studies to determine the etiological agent of the sensitivity were either omitted or were incomplete. These cases have been included in the general discussion which follows, but actually they cannot be accepted as proved instances of insulin sensitivity, since they may represent allergy to the pancreatic extract, contaminants in commercial preparations of the animal used, etc.

Walker,[7] in 1926, and Engelberg,[33] in 1927, each reported a case in which generalized urticaria and edema developed after insulin therapy. The reactions were immediate, but further difficulty was obviated by changes in dosage and by alteration of the site and time of administration.

In 1928, Tuft[38] presented an excellent review of insulin sensitivity and in addition reported a case of his own in which the patient was given insulin. Therapy was then omitted for eighteen months; on resumption the patient developed nausea, vomiting, generalized urticaria, and pruritus on the eleventh injection with 20 units. The symptoms began twenty minutes after injection and subsided by the end of an hour. Skin tests with insulin preparations, including the crystalline, were all positive.

During the 1929-1931 period, sporadic case reports appeared in the literature by Jeanneret[34] and Bonem[32] in France, Hallermann,[36] Stroomann,[35] and Kaufman[37] in Germany, and Blaisdell[31] in the United States, describing generalized urticaria and pruritus in patients receiving insulin. The case histories were given very briefly, and allergy studies such as direct skin testing or passive transfer tests were either omitted or incomplete. From the description, however, this group probably represented a series of cases possessing generalized sensitivity to commercial insulin, although one cannot say whether the sensitivity was caused by the insulin fraction or by the animal tissue portion. Campbell,[39] in 1930, described a case of marked sensitivity to both commercial and crystalline insulin, but failed to state whether the sensitivity was local or systemic. Grishaw[40] presented a carefully studied case of a patient sensitive to two commercial insulin preparations but not to a third. He concluded that the patient was not sensitive to insulin, but rather to some substance contained in the first two preparations. Crystalline studies were not done.

In 1932, Allen and Scherer[13] published a comprehensive report on insulin sensitivity and added four cases of their own. All showed

*One case each by Allen,[13] Blaisdell,[31] Bonem,[32] Engelberg,[33] Jeanneret,[34] Stroomann,[35] and Walker[7]; two cases by Hallermann[36]; and three cases by Kaufmann.[37]

generalized cutaneous manifestations and were positive to insulin skin tests. Two of the four patients were also tested with crystalline insulin, with positive results. In each case, after trying various methods to eliminate the sensitivity, insulin therapy had to be discontinued. Williams[41] reported two cases of severe gastrointestinal disturbances caused by insulin. One patient was relieved by switching from pork to beef insulin preparations, and the other was changed from beef to pork insulin, with good results. These cases represented sensitivity to the pancreatic tissue.

Johnson[42] has described arthritis as a possible manifestation of allergy to insulin. In his patient a polyarthritis developed one week after insulin therapy, subsided on the discontinuation of insulin, and was unaffected by salicylates. No allergy studies were done.

Six careful investigations of individual cases have appeared since 1932, one each by Bryce,[43] Davidson,[11] Sammis,[44] Herold,[2] Corcoran,[45] and Ulrich, Hooker and Smith.[46] Each patient received thorough skin tests and was shown to be sensitive to crystalline insulin. The patients of Bryce, Davidson, and Sammis eventually gave up insulin; Corcoran's case lost the sensitivity, and Herold was successful in desensitization.

The patient reported below is the first case encountered at the Boston City Hospital and is only the twelfth case reported in the literature in which the patient possessed a generalized sensitivity to insulin, with skin test confirmation.

CASE REPORT

H. M., a 43-year-old white female, was first seen in the diabetic clinic on Sept. 4, 1931. She entered for follow-up care of her diabetes which had been discovered a few weeks previously while she was on a surgical service of the Boston City Hospital for an appendectomy. For many years she had had asthma and on occasion had shown a sensitivity to various foods. While in the hospital she received insulin injections on several occasions and apparently showed no sensitivity. She was discharged on a diet alone, without insulin, and the diabetic state was well controlled. For five weeks she attended the diabetic clinic, and she then disappeared.

On May 15, 1939, she appeared in the surgical outpatient department because of a colicky pain in the right lower quadrant, associated with vomiting. Right kidney pathology was suspected. Because of her diabetic history, she was referred to the diabetic clinic where she appeared two days later. During her eight-year absence she had disregarded her diet and had not taken insulin, and her urine examination in the clinic showed a complete reduction of Benedict's solution with a one plus acetone. The patient was instructed in the use of a high carbohydrate, low fat diet, and was told to take 15 units of protamine insulin (Lilly U-40).

Seven days later she returned, complaining of a "reaction" from fifteen to thirty minutes after taking insulin, consisting of red swellings over the entire body, generalized pruritus, stiffness of the lips, dyspnea, sweating, and palpita-

tion. Swellings developed at the site of injection. The symptoms would subside in from thirty to forty-five minutes and disappear in about three hours. She was advised to take 10 units of protamine insulin (Squibb, instead of Lilly) each morning.

One week later she again returned, with a history of the same symptoms following insulin and a discontinuance of injections for the past three days. She was given 10 units of protamine insulin in the clinic, and a reaction similar to the one previously described was observed. Generalized urticaria, pruritus of the entire body, but most marked in the fingers and scalp, headache, constriction of the chest, dyspnea, and stiffness of the lips developed about fifteen minutes after injection and did not subside for another four hours.

During the next two weeks she was tried on pig, beef, and sheep preparations without success. Skin tests with all were markedly positive. A crystalline insulin preparation was obtained, but she showed a skin reaction to this, although not as marked as with the commercial preparations.

At present the patient is being controlled on diet alone, with moderate success. If, in the future, insulin is deemed advisable, desensitization will be attempted.

DISCUSSION

As seen in Table I, cases of sensitivity to insulin were observed in the older age group, the ages varying from 40 to 60 years, except for Herold's report in which the patient was a 23-year-old male. All but two of the twelve cases occurred in women. Although the incidence of allergic states is higher in females, still one cannot explain satisfactorily the overwhelming female predominance in this series.

In eight cases there was a definite history of allergy, either in the patients or in the parents. The most common backgrounds consisted of hay fever, asthma, and sensitivity to various foods. Two cases gave a negative history, and in the remaining two cases no mention of the past history was made.

All patients showed cutaneous manifestations of one sort or another. Urticaria was most frequent, being seen in 91 per cent of the cases, while itching or burning sensations were noted in seven cases, or 59 per cent. Edema of the face, distinct from urticaria, was noted in two instances.

Circulatory disturbances in the form of pallor, dyspnea, increased pulse rate, and general prostration were described in four patients, or 33 per cent, while one patient experienced gastrointestinal symptoms consisting of nausea and vomiting.

In three cases desensitization to insulin was effective and the patients were continuing insulin therapy at the time of the report. In every other case, however, further treatment with insulin was considered inadvisable for a variety of reasons. Three of these patients were nondiabetic patients who were receiving insulin in an effort to increase their weights, and the remaining four had insulin therapy discontinued by their physicians.

Since the severity of the disease in persons developing diabetes in the fifth to seventh decades often is mild, and since the great preponderance of cases showing generalized allergy to insulin were in the older age groups, the problem of insulin therapy is not as acute as in the young age group. Therefore, it is possible to discontinue insulin in many patients showing generalized sensitivity to the medication.

Except in one instance, the reactions came on before the twenty-fifth injection of insulin, and most were observed during the first twelve injections. It is interesting to note that in seven cases a lapse of insulin therapy for from a few months to a few years was allowed, and then on resuming treatments a generalized allergy was encountered. During the initial trial with insulin this allergy was absent or only slight and limited to the site of injection, but on resumption a generalized sensitivity occurred. While many diabetic patients gave a history of omitting insulin injections for varying intervals without untoward reactions, still it is significant that in this series under discussion more than one-half the cases (59 per cent) gave such a history of lapse of therapy. This finding of a history of insulin therapy followed by a period without therapy, and this in turn followed by development of generalized allergy on resumption of insulin, deserves emphasis, since it fits in with our present-day ideas of anaphylaxis and allergy. Perhaps a prophylactic measure in preventing insulin sensitivity would be the continuance of occasional small doses of insulin in patients with a history of allergy who have once begun injections, rather than the complete cessation with a possibility of resumption at a later date.

Nine patients (76 per cent) eventually discontinued the use of insulin. Three patients were desensitized successfully. Corcoran gave increasing doses every fifteen to twenty minutes for twelve hours, until fairly large amounts were tolerated, while Herold used the same principle but gave daily doses for three months before his patient tolerated therapeutic doses. Bryce also employed desensitization successfully, using daily and then twice-daily injections. A further study on desensitization in insulin allergy has been reported by Bayer.[47] Collens[21] has suggested repeated injections of histamine as a possible aid in insulin allergy, but his experience was limited entirely to cases with local reactions. Karr[48] has suggested treating an insulin-sensitive patient with the serum of a rabbit which had previously been sensitized with the patient's serum.

An interesting observation by Rudy,[49] Allen,[50] and others revealed that a development of insulin sensitivity may also be accompanied by insulin resistance on the part of the patient, thereby necessitating larger doses of insulin for control of the diabetes. With disappearance of the sensitivity, insulin resistance also subsides.

CONCLUSIONS

A review of the literature on allergy to insulin revealed: eleven cases of generalized sensitivity to crystalline insulin, confirmed by allergy studies; three cases of sensitivity to impurities contained in commercial insulin, confirmed by allergy studies; and twelve cases of suggestive sensitivity to insulin, without allergy studies.

The majority of cases occurred in people over 40 years of age with a history of allergy.

All cases showed cutaneous manifestations of allergy, while only a few exhibited circulatory or gastrointestinal symptoms.

The majority of cases had a history of lapse in therapy, with sensitivity developing on resumption of therapy.

Three cases were desensitized successfully; the remainder discontinued insulin.

The twelfth case of generalized sensitivity to insulin confirmed by allergy studies is reported.

I wish to thank Dr. Richard W. Ohler, Physician-in-Charge of the Diabetic Clinic of the Boston City Hospital, and Dr. Richard W. Stetson, Attending Physician of the Diabetic Clinic, for their valuable aid and advice in the preparation of this paper.

REFERENCES

1. Altshuler, S. S.: Crystalline Insulin; Clinical Use, Ann. Int. Med. **11**: 901, 1937.
2. Herold, A. A.: Insulin Allergy; Severe Case With Successful Desensitization, New Orleans M. & S. J. **91**: 163, 1938.
3. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, 1937, Lea & Febiger.
4. Kern, R. A.: Studies in Heredity in Allergy and in Diabetes, Tr. Assn. Am. Phys. **49**: 23, 1934.
5. Abel, J. J., and Geiling, E. M. K.: Crystalline Insulin, J. Pharmacol. & Exper. Therap. **25**: 423, 1925.
6. Abel, J. J., and Geiling, E. M. K.: Ibid. **31**: 65, 1927.
7. Walker, S. E.: Report of a Case of Diabetes Mellitus With Anaphylaxis Following the Hypodermic Injection of Insulin, U. S. Vet. Bur. M. Bull. **2**: 700, 1926.
8. Lewis, J. H.: The Antigenic Qualities of Insulin, J. A. M. A. **108**: 1336, 1937.
9. Hagedorn, H. C.: Presentation at Nordisk Congress for Internal Medicine, Copenhagen, June 29, 1935.
10. Allen, F. N., and Scherer, L. R.: Insulin Allergy, Proc. Staff Meet. Mayo Clin. **8**: 204, 1932.
11. Davidson, M. T.: Insulin Sensitivity; Case Report, J. ALLERGY **6**: 71, 1934.
12. Bernstein, C., Kirsner, J. B., and Turner, W. J.: Studies on Anaphylaxis With Insulin, J. Lab. & Clin. Med. **23**: 944, 1938.
13. Allen, F. N., and Scherer, L. R.: Insulin Allergy, Endocrinology **16**: 417, 1932.
14. Cornil, L.: Circumscribed Lipo-Atrophy Caused by Insulin, Presse méd. **46**: 1282, 1938.
15. von Schoonhoven van Beurden, A. J. R. E.: Local Lipo-Dystrophy as a Result of Prolonged Insulin Injections, Geneesk. gids **16**: 583, 1938.
16. Leger, A.: Lipo-Dystrophy Following Four Years of Therapy; Case, Union méd. du Canada **67**: 17, 1938.

17. Bertram, F., and Never, H. E.: Lipo-Dystrophy Due to Insulin Therapy of Diabetes, Med. Welt **13**: 150, 1939.
18. Stotter, G.: Successful Desensitization in a Patient With a High Degree of Allergy, Klin. Wchnschr. **16**: 1180, 1937.
19. Lawrence, R. D.: Local Insulin Reactions, Lancet **1**: 1125, 1925.
20. Rackemann, F. M.: Clinical Allergy, Particularly Asthma and Hay Fever, New York, 1931, Macmillan Co., p. 192.
21. Collens, W. S., Lerner, G., and Fialka, S. M.: Insulin Allergy: Treatment With Histamine, Am. J. M. Sc. **188**: 528, 1934.
22. Williams, J. R.: Clinical Study of Effects of Insulin in Severe Diabetes, J. Metabolic Research **2**: 729, 1922.
23. Wilder, R. M., Boothby, W. M., Barborka, C. J., Kitchen, H. O., and Adams, S. F.: Clinical Observations on Insulin, J. Metabolic Research **2**: 701, 1922.
24. Joslin, E. P., Gray, H., and Root, H.: Insulin in Hospital and Home, J. Metabolic Research **2**: 651, 1922.
25. Geyelin, R.: Use of Insulin in Juvenile Diabetes, J. Metabolic Research **2**: 767, 1922.
26. Lereboullet, P., Lelong, M., and Erossard, R.: Eruptions Under Insulin Treatment, Bull. et mém. Soc. méd. d. hôp. de Paris **48**: 1184, 1924.
27. Mauriac, M., quoted by Blamoutier, P.: A Case of Sensitivity to Insulin in a Child, Paris méd. **55**: 372, 1925.
28. Umber, F., and Rosenberg, M.: Insulin Treatment, Deutsche. med. Wchnschr. **50**: 359, 1924.
29. Raymond, A., and La Croix, A.: Un cas d'anaphylaxie a l'insuline, Bull. et mém. Soc. méd. d. hôp. de Paris **49**: 831, 1925.
30. Achard, C., and Bloch, S.: Diabête avec coma guéri par l'insuline: Accidents d'anaphylaxie et pyohémie consécutive, Bull. et mém. Soc. méd. d. hôp. de Paris **49**: 1210, 1925.
31. Blaisdell, E. R.: Allergic Reactions, Maine M. J. **22**: 129, 1931.
32. Bonem, P.: Nebenwirkungen von Insulin, München. med. Wchnschr. **76**: 1585, 1929.
33. Engelberg, J.: A Case of Insulin Sensitivity, Med. Klin. **23**: 212, 1927.
34. Jeanneret, R.: Une application pratique de la méthode de désensibilisation par les cutiréactions répétées: Urticaire à l'insuline, Rev. méd. de la Suisse Rom. **49**: 99, 1929.
35. Stroomann, G.: Anaphylaktische Erscheinungen nach Injektion von Insulin, Med. Klin. **26**: 1523, 1930.
36. Hallermann, A.: Nebenerscheinungen bei der Insulinanwendung, Deutsch. med. Wchnschr. **56**: 1611, 1930.
37. Kaufmann, E.: Deutsche. med. Wchnschr. **56**: 1955, 1930.
38. Tuft, L.: Insulin Hypersensitiveness: Immunological Considerations and Case Report, Am. J. M. Sc. **176**: 707, 1928.
39. Campbell, W. R., Gardiner, W. J., and Scott, D. A.: Reactions After Administration of Crystalline Insulin, J. Clin. Investigation **9**: 28, 1930.
40. Grishaw, W. H.: Allergic Manifestations to Insulin, J. A. M. A. **97**: 1885, 1931.
41. Williams, J. R.: A Second Case of Gastro-Intestinal Allergy Due to Insulin, J. A. M. A. **100**: 658, 1933.
42. Johnson, A. S.: Arthritis as a Possible Manifestation of Allergy to Insulin, New England J. Med. **211**: 321, 1934.
43. Bryce, L. M.: Hypersensitiveness to Insulin, M. J. Australia **1**: 371, 1933.
44. Sammis, F. E.: Insulin Allergy: Case Report, J. ALLERGY **6**: 387, 1935.
45. Corcoran, A. C.: Rapid Desensitization in a Case of Hypersensitiveness to Insulin, Am. J. M. Sc. **196**: 359, 1938.
46. Ulrich, H., Hooker, S. B., and Smith, H. H.: Allergic Response to Insulin, New England J. Med. **221**: 522, 1939.
47. Bayer, L. M.: Desensitization to Insulin Allergy, J. A. M. A. **102**: 1934, 1934.
48. Karr, W. J., Kreidler, W. A., Scull, C. W., and Petty, O. H.: Certain Immunological Studies in Insulin Sensitivity, Am. J. M. Sc. **181**: 293, 1931.
49. Rudy, A.: Urticaria and Insulin Resistance With Reference to the Relation of the Skin to Carbohydrate Metabolism, New England J. Med. **204**: 791, 1931.

50. Allen, F., and Scherer, R.: Insulin Resistance Due to Allergy, Am. J. M. Sc. **185**: 815, 1933.
51. Rivoire, R., and Pozzo-di Borgo, C. A.: A Case With Extreme Insulin Sensitivity Treated With Protamine Insulin, Bull. et mém. Soc. méd. d. hôp. de Paris **53**: 1434, 1937.
52. Masek, J., and Klir, C.: Hypersensitivity: Clinical and Experimental Study, Ann. de méd. **41**: 301, 1937.
53. Nadler, W. H.: Sensitiveness to Insulin and Optimal Diets in Diabetes, Arch. Path. **26**: 395, 1938.

340 Walnut Avenue
Roxbury, Mass.

ATMOSPHERIC ALLERGENS IN ALASKA

O. C. DURHAM
NORTH CHICAGO, ILL.

DURING July, August, and September, 1939, daily tests of the pollen and spore contents of the air were made in Nome, Fairbanks, and Juneau, Alaska. Slide samples were secured by the cooperation of local observers of the United States Weather Bureau, and counting was carried out by the same methods employed by the writer in previously published atmospheric surveys. This study embraces the northernmost territory yet included in any known pollen survey and was made for the purpose of supplementing the recorded data on the incidence of air-borne allergens in the United States, Canada, and Mexico. The primary purpose was to determine the presence or absence of ragweed in the area.

The total number of significant air-borne particles found on all 276 slides was comparatively small. It was much less than frequently is found on a single twenty-four-hour slide in the agricultural areas of the United States. Fairbanks, the northernmost of the 3 stations, and the only inland point, had the fewest pollen grains and by far the most spores. Nome had the fewest spores and the most pollen.

No ragweed pollen was found on any of the slides.

TABLE I

POLLEN COUNTS

	GRASS	CHENOPOD	PINE	SEDGE	COMPOSITE	SAGE	MISCELLANEOUS	TOTAL
Juneau	66	0	10	5	3	0	43	127
Fairbanks	28	29	0	0	0	11	8	76
Nome	164	0	0	0	0	12	0	176

Grass pollen, which constituted more than two-thirds of all pollen encountered, was sufficiently abundant in each place to mark a definite season of pollination. This occurred during the first two weeks of July in Juneau and Fairbanks and during the last week of July and the first 2 weeks of August at Nome. It is probable that the grass season starts in June at Juneau, and perhaps even at Fairbanks. The exposures were not begun soon enough to make sure of this point. Possibly Juneau has a grass season comparable in time to that of Seattle.

Tree pollen was noted only at Juneau where small amounts, including a little pine, appeared on the slides almost every day during the first 2 weeks of August.

A very few sagebrush pollens were noted during the latter part of July at Nome and Fairbanks, but not at Juneau. There were certainly

Read before the Annual Meeting of the American Association for the Study of Allergy, New York, N. Y., June 10, 1940.

not enough of these to cause inconvenience to a ragweed-sensitive person who might find it necessary to live in such locations during the summer months.

TABLE II

FUNGUS SPORE COUNTS

	ALTERNARIA	HORMODENDRUM	PENICILLIUM	RUST	SMUT	FUSARIUM	MISCELLANEOUS	TOTAL
Juneau	0	0	x	24	25	0	27	76
Fairbanks	11	163	0	529	4	3	26	736
Nome	0	0	0	4	0	0	5	9

x, Not counted.

Chenopod pollen was caught only during the grass season and only at Fairbanks. The amount was insignificant.

Brake spores were present in small amounts during September in Juneau, but not at all in the 2 other stations. These air-borne particles are more numerous in the air in Puget Sound and western Oregon areas during August and September than any other kind of spore or pollen, but are reported to be of no clinical significance.

Two-thirds of the fungus spore catch was from rust, and nearly all of this was caught at Fairbanks. Considering the lack of clinical activity of this spore in other places, the finding may be regarded as unimportant. *Penicillium,* found only at Juneau and on only three days, was next in abundance, but because of the tendency of this mold to grow on oiled slides, no count was attempted.

TABLE III

TOTAL AIR-BORNE ALLERGENS

	POLLENS	LYCOPODIUM SPORES	BRAKE SPORES	FUNGUS SPORES	TOTAL
Juneau	127	0	55	76	258
Fairbanks	76	13	0	736	825
Nome	176	0	0	9	185

Alternaria and *Hormodendrum* were found only at Fairbanks. The former were as a trace, and the latter only up to a maximum of 33 spores in one day.

Smut and *Lycopodium* spores at Juneau and Fairbanks were so few as to be of academic interest only.

From this report, the possibility of inhalant allergy from pollen and spores in Alaska is remote or is confined, at most, to a few days of light exposure to grass pollen in late June and early July in southern and central Alaska, and a month later in the vicinity of Nome.

DISCUSSION

DR. F. W. WITTICH, Minneapolis.—Mr. Durham's careful survey covered 3 of the most representative areas in Alaska and no doubt gives the first fundamental information upon which clinical observations can be

made. Alaska covers a larger seasonal variety of vegetation than most realize, and we have reasons to believe that further surveys will, no doubt, show this.

Poplars, *Calamagrostis canadensis,* bracken fern, and members of the raspberry tribe predominate. There is much grassland on the coast, and oats are grown in Matanuska Valley. Timothy and red top are grown for hay. The spores of bracken referred to are the normal asexual spores of this fern, which mature in the fall and winter, and not the spores of any molds on it. There are at least 5 species of rust and 4 of common air molds infesting bracken: *Pteridium, Cladosporium, Fusarium,* and *Septoria.*

Mr. Durham's surveys showed grass pollens, rusts, *Hormodendrum,* and smuts to predominate. In other regions of the Pacific Northwest, grass smuts are the predominating smuts, especially since grain smuts are getting under control.

During June, July, August, and part of September, the air contains liberal amounts of spores of head smut of grasses, *Ustilago bullata,* especially from cheat grass, *Bromus tectorum.* The heads of this grass are from 20 to 80 per cent smutted.

Benson mentions a local case of allergy in an 11-year-old boy which was attributed to wheat smut. It is reasonable to conclude from these observations that molds as well as pollens may be suspected as offenders in this region.

These surveys may assume particular importance if our present European war continues, when Canada and no doubt Alaska become more thickly settled with migrating refugees.

DR. WARREN T. VAUGHAN, Richmond.—I should like to ask Mr. Durham one question. About 1929, I found the statement, and I have requoted it several times although I cannot even remember where I originally found it, that either spores or pollens have been found in Washington and Oregon which were known to have come from Alaska, thus demonstrating the great distances to which these can be carried. Did you, in your experience, find any unusual spores or pollens that might be identified as having come especially from Alaska?

MR. DURHAM.—No, I have not seen that statement; I do not know where it could have come from. I know nothing about this.

DR. ALEXANDER STERLING, Philadelphia.—May I ask Mr. Durham if there is any clinical evidence of the presence of hay fever or of hay fever and asthma in Alaska.

MR. DURHAM.—I did not investigate the clinical angle. I know of no allergist up there.

Special Reports

MANGO DERMATITIS

AARON BROWN, M.D., AND FREDERICK R. BROWN, M.D.
NEW YORK, N. Y.

MANGO *(Magnifera,* family *Anacardiaceae),* a member of the family to which the cashew and pistachio nuts, poison ivy, and poison oak also belong, is a native tree of southern Asia, and from there it has been distributed throughout the tropics of both hemispheres. The most common is *Magnifera indica,* varieties of which have, within the past twenty-five years, been introduced into southern California and southern Florida. The mango tree may grow to a height of 40 feet, and it is valued both for its shade and for the fruit it produces. The fruit is oval and varies in weight from 4 to 32 oz. It has a yellowish-green peel, with a pulp resembling that of an orange, and the seed is large, flat, and almost as long as the fruit itself. Mangos are coming into wider use in the United States.

For a long time, the fruit was suspected as the cause of the skin rashes appearing in the fruiting season. In 1914, Isabella Concepción[1] reported the appearance of a skin rash on the lips, face, and arms of a series of patients to whom she fed from four to six mangos daily. While mangos had been suspected as a causal factor, many believed that, since the rash was prevalent during hot weather, heat and insect bites were the responsible agents. Concepción's experiment proved the relationship of mangos to the dermatitis.

Simmons and Bolin,[2] in 1921, in a well-written article, concluded that the rash of mangos was due to a nonprotein skin irritant present in the sap of the tree and in the peel of the fruit. They also stated that all varieties of the fruit can produce the skin lesions, that there is difference in susceptibility, and that the peeled fruit could be eaten with impunity.

In 1938, Kirby-Smith[3] gave a fine review of the subject and proved by patch tests with the peel that the resin was responsible for the dermatitis.

The usual type of rash is a vesicular eruption appearing on the lips, face, and hands within from six to twenty-four hours after handling or eating the fruit or coming into contact with the sap of the tree. The eruption lasts from one to two weeks. Sometimes, a stomatitis and, more rarely, acute gastrointestinal symptoms appear.

From the Department of Medicine, New York University College of Medicine.

CASE REPORT

Miss C. L., 19 years old, appeared at the Allergy Clinic of the New York University College of Medicine in April, 1939, with a vesicular eruption on her lips and face of several days' duration. She reported having eaten mangos several days previously. A year before, while she was in Cuba, the eating of mangos had produced similar lesions, but she stated that she ate peeled mangos without any harmful effect. The patient was very susceptible to poison ivy. The rash which brought her to the clinic cleared up in a few days without any special treatment. A scratch test with mango pulp was negative, but a patch test with the peel gave a positive reaction in forty-eight hours.

The peel and pulp of six mangos were extracted separately with anhydrous ether in a Soxhlet apparatus to remove fat. The peel yielded a yellowish wax like oil, but none was obtained from the pulp. The pulp was dialyzed in a cellophane bag against tap water and then against Coca's extracting fluid, neutralized, and sterilized by Seitz filtration. The total nitrogen content of the pulp extract was 0.7 mg. nitrogen per cubic centimeter.

Intracutaneous tests with pulp extract, even in the concentrated form, were negative. Patch tests with the oil, however, were positive, with the production of a vesicular eruption in forty-eight hours. Patch tests with the oil in seven other subjects were negative.

Brown, Milford, and Coca[4] showed that the oil of ragweed pollen and not the atopic excitant was responsible for the dermatitis that sometimes occurs during the ragweed pollinating season.

With mango dermatitis the situation is similar, in that the oil and not the protein element is responsible for the contact dermatitis.

REFERENCES

1. Concepción, Isabella: Observation on Mango Rash, Phillipine J. Sc. **9**: 509, 1914.
2. Simmons, J. S., and Bolin, Z. E.: Dermatitis Venenata Produced by an Irritant Present in the Stem and Sap of the Mango (Magnifera Indica L.), Am. J. Trop. Med. **1**: 351, 1921.
3. Kirby-Smith, J. L.: Mango Dermatitis, Am. J. Trop. Med. **18**: 373, 1938.
4. Brown, A., Milford, E. L., and Coca, A. F.: Studies in Contact Dermatitis: The Nature and Etiology of Pollen Dermatitis, J. ALLERGY **2**: 301, 1931.

VASOMOTOR RHINITIS AND ASTHMA DUE TO PAPRIKA

Case Report

H. Harold Gelfand, M.D.
New York, N. Y.

IN A SEARCH of the literature, no record of allergic manifestations similar to those here reported was found. De Kovats[1] cites the case of a young girl with chronic cough and expectoration attributed to paprika dust in the factory where she worked. It is not clear that this was a paprika sensitization.

CASE REPORT

B. G., aged 20 years, was employed part time as a bookkeeper in a wholesale spice store, beginning in January, 1938. All types of spices were sold. Although the patient worked as a bookkeeper, it was necessary for him to be in frequent contact with the clerks who weighed and measured powdered spices, and at times he was also called upon to handle these products.

During a period of six months (to June, 1938) of employment in this store he noticed that whenever he handled paprika he sneezed and his nose became clogged. These symptoms became progressively worse in the course of ten months, and finally after sixteen months of occupational contact with the paprika (May, 1939) he began to notice a slight cough in the morning and at night. The nasal symptoms finally became so severe and continuous that in June, 1939, he consulted a rhinologist. The first sign of heaviness on the chest and a pronounced cough were observed in September, 1939.

Table I

DILUTIONS		NEUTRALIZATION		
SERUM DILUTION	REACTIONS ON TEST WITH 1,000 UNITS PER C.C. PAPRIKA EXTRACT	SERUM MIXED WITH	PROTEIN NITROGEN UNITS PER C.C.	TESTED 48 HOURS LATER WITH PAPRIKA, 1,000 UNITS PER C.C.
Concentrated	++++	Paprika	100	++
1:10	+++	Paprika	300	+
1:100	++	Paprika	1,000	0
1:1,000	+	Paprika	Saline	++++
1:10,000	0			

The chest symptoms, cough and wheezing, increased in severity and even resulted in definite attacks of asthma in November, 1939, twenty-two months after he first started work in the spice store. By December, 1939, the asthmatic attacks became so severe that it was necessary for him to stop work. Immediately upon his removal from his occupational environment, all the symptoms ceased.

Roentgenograms of the chest revealed increase in hilar shadow and peribronchial thickening, with no parenchymal involvement.

By direct intradermal test with paprika (100 units protein nitrogen per cubic centimeter), a positive reaction was obtained.

From the Department of Allergy, The Roosevelt Hospital, New York.

For the passive transfer study* a paprika extract was prepared and standardized on a protein nitrogen basis.

Passive transfer test sites were also prepared and tested forty-eight hours later with 0.02 c.c. of the following extracts containing 100 protein nitrogen units per cubic centimeter: allspice, cinnamon, black pepper, clove, ginger, mace, sage, thyme, coffee, tea, and vanilla. These gave negative reactions.

The gradual development of the symptoms in the case reported here tends to support the hypothesis that this patient acquired sensitivity to paprika from occupational contact.

REFERENCE

1. de Kovats, F.: Diffuse Bronchio-Alveolititis From Capsicum, Arch. méd.-chir. de l'app. respir. 7: 58, 1932.

*These tests were carried out in the laboratory of the Allergy Clinic of The Roosevelt Hospital, New York.

A SIMPLE APPARATUS FOR EXTRACTING TOBACCO SMOKE

David M. Pipes, M.D.
Greensboro, N. C.

DETAILED accounts of extracting tobacco smoke are lacking in the medical literature. Earlier methods embodied the principle of bubbling smoke through an extracting medium, usually glycerosaline, either by suction or positive pressure.

Vaughan used both methods. His first efforts at tobacco smoke extracting consisted in blowing cigar smoke into a rubber tube which led to a bottle containing glycerosaline. Later, he extracted cigar smoke by the suction principle, using an ordinary water suction pump attached to an apparatus similar to the one described here. The apparatus used by the author is suggested by Vaughan's method and also incorporates some principles of tobacco smoke extracting as used by the American Tobacco Company.

The suction method is used. Instead of bubbling tobacco smoke through the extracting medium, it is drawn into an Erlenmeyer flask over glycerosaline and permitted to "settle out."

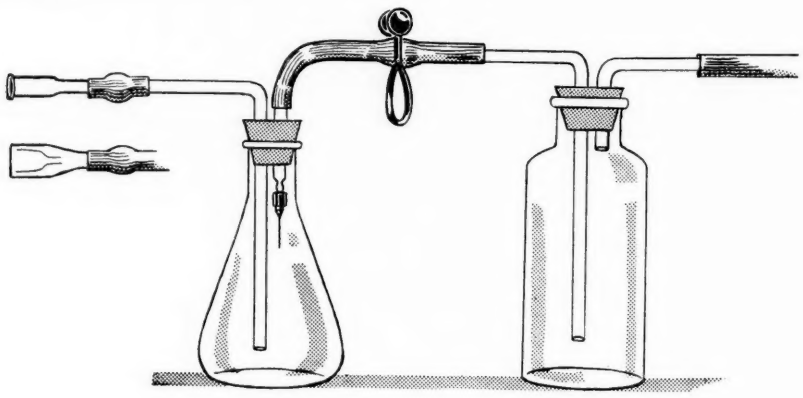

Fig. 1.

The apparatus consists essentially of a cigarette holder or cigar holder connected by a short length of rubber tubing to a right angle glass tube leading down into a 250 ml. Erlenmeyer flask through a two-hole rubber stopper. This right angle tube constitutes the inlet (Fig. 1). The outlet consists of an 18 gauge needle attached to a glass adapter which passes through the two-hole rubber stopper and is connected with a trap bottle by means of rubber tubing. The trap bottle in turn leads to a water suction pump. The rubber tubing between the Erlenmeyer flask and the trap bottle is closed by a pinchcock.

To carry out the extraction, glycerosaline is used, roughly in the ratio of 1 c.c. to one cigarette, or 35 c.c. to one cigar. After the cigarette or cigar is placed in its appropriate holder, the suction pump is put in operation by turning on the water faucet. At this point the pinchcock between the Erlenmeyer flask and the trap bottle is closed. The cigarette or cigar is lit by releasing the pinchcock and applying a lighted match. During the process of extraction the pinchcock is held open at two-minute intervals, with suction being maintained not longer than twenty seconds. Thus the apparatus is made to puff the cigarette or cigar for twenty seconds every two minutes. The 18 gauge needle acts as both a pressure governor and a trap to retain smoke within the Erlenmeyer flask.

After the desired number of cigarettes or cigars have been smoked over the proportionate amount of extracting fluid, the apparatus is allowed to stand intact for about thirty minutes, permitting smoke hovering over the extracting fluid to "settle out."

To clean the unit, ordinary rubbing alcohol may be used, followed by a thorough rinsing with tap water. It should be permitted to dry before it is used again.

101 North Elm Street

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D., CHICAGO

A New Type of Medication to Be Used in Bronchial Asthma and Other Allergic Conditions: Preliminary Note. Brown, E. A.: New England J. Med. 223: 843, 1940.

Tablets containing ephedrine, phenobarbital, and theophylline were given an enteric coating so that they would not disintegrate for a period of three and one-half to five hours. The main purpose of this type of medication was its use in nocturnal asthma. Attacks during the night or early morning hours could usually be prevented by the administration of a coated tablet at bedtime. In some instances, it was found wise to administer a gelatin capsule containing the same medication along with the tablet intended for delayed action. Oftentimes such nightly medication had the effect of reducing the likelihood of asthma during the day.

Possible Relation Between Electrolyte Balance and Bronchial Asthma. Stoesser, A. V., and Cook, M. M.: Am. J. Dis. Child. 60: 1252, 1940.

Studies on electrolyte balance were made on twelve asthmatic children. The addition of 6 to 10 Gm. potassium chloride daily to a special low-salt diet produced relief from the milder attacks of asthma. Administration of the potassium salt during remissions did not cause a recurrence of the asthma. Severe attacks of asthma continued while the potassium was administered, but the attacks stopped when the salt was discontinued.

Fever therapy gave strikingly beneficial results in the asthmatic patients when the diet was kept low in salt, less than 200 mg. of sodium daily. If the sodium chloride intake is normal or high before or during fever treatment, the relief is transient. These authors also found that remissions due to artificial fever plus low salt intake could be promptly terminated by the addition of 1 or 2 Gm. of sodium chloride to the diet.

Blood Potassium Studies in Allergic States. Parker, F. P.: South. M. J. 33: 1301, 1940.

In a series of thirty-four patients with asthma, hay fever, perennial rhinitis, urticaria, and eczema, twenty-two (64.7 per cent) showed marked or complete relief following the use of potassium chloride or gluconate. The effective daily doses of the chloride varied from 10 to 60 grains. Serum potassium studies showed normal figures in allergic persons. The level of serum potassium did not show any appreciable increase after oral potassium therapy. The author concludes that this failure in the rise of serum potassium suggests the occurrence of more effective increase of the tissue potassium concentration.

The Nature of Various Mill Dust Allergens. Wittich, F. W.: Lancet 60: 418, 1940.

Wittich reports a four-year survey and study on the nature of the dusts from grain and flour mills as allergens. Mill dusts may owe their allergenic nature to any of a number of sources; the grains themselves, smuts, rusts, common air molds, and insects. The various fractions enumerated were tested by means of skin reaction, nasal and conjunctival tests, passive transfer, Dale and anaphylactic shock. By such means the allergenic and antigenic properties of these components were confirmed. The author found that a properly selected mill dust produced clinical desensitization in 85 per cent of the patients who showed reactions to the individual components.

A Qualitative and Quantitative Study of Atmospheric Pollen at Moscow, Idaho. Daubenmire, Jean B.: J. Lab. & Clin. Med. 26: 311, 1940.

Daubenmire studied the pollen content of the air in Moscow, Idaho, during 1938. The figures are reported on the basis of an area of 3.24 sq. cm.(?) Grasses gave the largest maximum count (214), and their pollen was present from the beginning of March to the middle of November. The chenopod-amaranth group produced pollen from the middle of March to the middle of November, with a maximum count of 62. Artemisia pollinated during approximately the same season, with a maximum count of 150. The ragweeds and false ragweeds pollinated from June to the middle of November, although the maximum daily count rarely exceeded 5. The majority of the other pollens were those of trees.

A Contribution to the Study of Pollinosis in the Argentine Republic. A New Plant Allergen: The Celtis Tala. Walker, H., and Carron, R. F.: Día méd. (special edition) No. 6, p. 140, August, 1940.

The authors describe a plant, *Celtis tala,* which they state sheds as much pollen into the air in certain portions of South America as the ragweeds do in certain portions of North America. This plant belongs to the *Ulmaceae* family and occurs in the form of trees or bushes. The plant is widespread, but most abundant in the central zone of Argentina in the northern parts of the provinces of Buenos Aires, Santa Fé, and Cordoba.

The pollen is from 20 to 25 μ in diameter, is imperfectly spherical, and has three slightly conical projections caused by a thickening of the external membrane. The plant begins to pollinate in September, reaches a maximum in November and December, and may continue pollinating, according to the latitude, until the middle of February. Sensitivity was frequently observed by the authors, who found that this pollen was the chief offender in 44 per cent of the patients with hay fever and 30 per cent of those with respiratory allergies whom they examined.

Studies With Antigens. VI. The Significance of Scratch Test Reactions to Purified House Dust Extracts. Efron, B. G., Boatner, C. H., and Pabst, M. R.: J. Invest. Dermat. 3: 401, 1940.

The authors have recently reported a purified house dust extract, prepared by a technique of precipitation of crude house dust extract by an optimum percentage of acetone or dioxane, and subsequent dialysis. The purpose of this investigation was to evaluate the significance of scratch test reactions produced by these purified house dust extracts. Two groups were selected. The first of 200 consecutive

cases gave a history negative of past or present allergy. The second was a group of 160 consecutive patients with perennial asthma or rhinitis, or both, although their allergy was not necessarily due to house dust. Scratch tests on the first group gave a percentage of from 7 to 8.5 reacting, depending upon the concentration, of house dust extract; in the second group from 75.6 to 78.75 per cent reacted. The low incidence of positive reactions in the control group indicates that the house dust extract is not a primary irritant. The conclusion is drawn that the purified house dust extract used in this way is diagnostic of house dust sensitivity in from 90.26 to 91.53 per cent of instances.

The Thyroid in Allergy. Barnes, M. C.: South. M. J. **33**: 1310, 1940.

In a study of twenty-five allergic patients blood cholesterol determinations and basal metabolism rates were found to be within the range of variations found in non-allergic groups.

Blood Serum Magnesium in Bronchial Asthma and Its Treatment by the Administration of Magnesium Sulfate. Haury, V. G.: J. Lab. & Clin. Med. **26**: 340, 1940.

Since it had been previously shown that magnesium salts can protect animals against anaphylactic shock, the author conceived the idea that there might be a similar relationship between magnesium and bronchial asthma. In a series of normal students he found a magnesium range of 1.74 to 3.10 mg. per 100 c.c. of serum, with a mean value of 2.33 mg. Sixty-six asthmatic subjects were studied. In twenty-six, determinations were made during acute attacks and in these the magnesium values ran from 1.10 to 3.1, with a mean value of 1.82. In 50 per cent of these the figures were below the lowest normal figures. Those asthmatics who were in the symptom-free period showed normal magnesium figures. Two hospitalized patients having asthma, which was only relieved at times by epinephrin given every four to six hours, showed a low magnesium level. At the height of the asthmatic paroxysm 20 c.c. of 10 per cent magnesium sulfate were given intravenously and 4 c.c. of the 50 per cent solution were given deep intramuscularly. Both patients were relieved immediately and remained free from symptoms for eighteen and twenty-four hours, respectively. The author concludes that a disturbance in magnesium metabolism may be a contributing factor in some patients suffering from asthma.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

Fixed Eruptions Due to the Arsphenamines. Chargin, L., and Leifer, W.: J. Invest. Dermat. **3**: 443, 1940.

This paper reports statistics on sixty-eight patients with fixed eruptions produced by trivalent arsenicals. Multiple tests with various members of this group of drugs showed that there was a sensitivity to several in many instances. The precipitating drugs were in order: arsphenamine, neoarsphenamine, silver arsphenamine, mapharsen, and trisodarsen.

Patch tests were uniformly negative both on unaffected and previously affected areas. Other drugs which commonly produced fixed eruptions did not activate the

lesions in any instance. Exfoliative dermatitis was not found in this group in spite of the fact that arsenical drugs were continued, in most instances with repeated flares of the fixed eruptions.

Eczema in Infants and Young Children. Hill, L. W.: New England J. Med. **223**: 624, 1940.

The author points out that although most infantile eczema has an allergic background, there are many factors which contribute to its development. Among these are fungous or pyogenic infections, contact with organic or inorganic substances, and chemical and mechanical irritation. Milk and wheat are the two most important allergens concerned with atopic eczema in the infant. In dealing with milk sensitivity, the author has found goat milk or a milk free food (soy bean meal) of value. For the most part he has found evaporated cows' milk to be of no value. Sensitivity to environmental agents has been uncommon, except for sensitivity to feathers.

Older children more frequently present sensitivity to environmental allergens, particularly to house dust.

Protective Ointment for the Prevention of Poison Ivy Dermatitis. Schwartz, L., Warren, L. H., and Goldman, F. H.: Pub. Health Rep. **55**: 1327, 1940.

The authors theorized that oxidation of the active principle of poison ivy (urushiol) would render this substance harmless to the skin of individuals susceptible to poison ivy. Tests on human volunteers with a concentrated active poison ivy extract demonstrated that the application of a vanishing cream containing 10 per cent sodium perborate resulted in protection of the skin of susceptible individuals both from active extracts and from natural poison ivy leaf.

As a practical procedure the authors recommend that the sodium perborate cream should be rubbed well into the skin of the arms and face of workers before exposure to poison ivy. This procedure leaves a deposit of the powdered oxidant on the skin.

"The protective cream should be allowed to remain on until the noon hour when it should be removed by washing with soap and water; this will emulsify the vanishing cream in the pores of the skin and wash away from within outward whatever toxin may be in the pores or in the skin.

"The cream should be reapplied again after the lunch hour and again washed off in the evening after the work is over.

"This vanishing cream should be freshly prepared at least once in two weeks to avoid deterioration."

Cutaneous Hypersensitivity to Iodine. Jacobs, J. L., and Colmes, A.: J. Lab. & Clin. Med. **26**: 302, 1940.

The subject of this study was hypersensitivity to tincture of iodine. Local application had for five years resulted in redness and vesiculation in the area treated. Patch tests with 0.5 per cent iodine in vaseline and with tincture of iodine gave positive delayed reactions. Those with 5 per cent iodine in alcohol and with a saturated solution of potassium iodide were negative. Intracutaneous tests with dilute iodine solution, potassium iodide, and diiodotyrosine were negative, as were intracutaneous and patch tests with iodinated human serum.

The authors point out that the negative patch tests to 5 per cent iodine in alcohol must not be given too much weight, for they were done with a minimal quantity of material, in order to avoid severe reactions in a very sensitive patient.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND
MAX HARTEN, M.D., BROOKLYN

The Action of Anesthesia on the Histamine Release in Anaphylactic Shock. Katz, G.: Am. J. Physiol. **129**: 735, 1940.

Isolated lung preparations from sensitized guinea pigs, perfused with specific antigen, released no detectable amounts of histamine when the perfusion fluid contained ether or urethane in concentrations above 0.25 per cent. Similarly, no histamine could be detected in "shock fluid" obtained from the incubation of sensitive lung or uterus with specific antigen if these tissues had had previous contact with ether or urethane. Furthermore, it was determined experimentally that the suppression of histamine release was not due to the action of the anesthetic on the antigen. The author concludes that the outstanding effect of the anesthetic in anaphylactic shock is the suppression of histamine release.

Observations on Sensitization of Guinea Pigs With Alum-Precipitated Ragweed Extract. Coulson, E. J., and Stevens, H.: Proc. Soc. Exper. Biol. & Med. **45**: 798, 1940.

After an incubation period of thirty days, guinea pigs sensitized with the whole alum-treated ragweed extract regularly responded with anaphylactic shock upon the intravenous administration of a water extract of ragweed pollen. It was found that the antigenic constituents were not completely precipitated by the alum.

Thirty-three days after sensitization with alum-precipitated ragweed extract the nodules resulting from the sensitizing injection were removed. Nodules from two or three animals were pooled, triturated in 0.9 per cent sodium chloride, and injected subcutaneously into normal guinea pigs. Anaphylactic symptoms could then be induced in these animals after an incubation period of from twenty-eight to thirty-two days.

These experiments indicate that alum considerably delays absorption and that the original antigenic substance present in the nodule remains in practically an unchanged condition for a long period of time. The continuous stimulation exerted by the slowly absorbed antigen probably accounts for the enhanced antigenic potency of the pollen extract.

Anaphylactic Shock and Nitrogen Metabolism in the Dog. Miller, L. L.: J. Biol. Chem. **133**: 93, 1940.

Anaphylactic shock in dogs results in increased urinary nitrogen excretion and parallels in degree the intensity of the anaphylactic symptoms. The response is comparable to that resulting from obvious tissue injury, e.g., sterile abscess. These findings support the view that anaphylactic shock may be marked by tissue injury of great severity. The increased creatine and uric acid excretion following anaphylactic shock in the dog supports the contention that both muscle and liver tissue undergo injury in shock in this animal.

The Failure of Histaminase to Protect Guinea Pigs Against Histamine and Anaphylactic Shock. Alexander, H. L., and Bottom, D.: J. Immunol. **39**: 457, 1940.

Histaminase requires several hours for the complete inactivation of histamine in vitro. Experiments with histaminase in animals indicate that its action in vivo is considerably accelerated. In the rabbit a marked lowering of the histamine-content of the blood may be observed within two hours after histaminase treatment. In

experiments recently reported by Karady and Brown, histaminase given fifteen minutes before testing was said to protect guinea pigs, in many instances, against lethal doses of histamine. Sensitized animals could be protected in a similar manner against fatal anaphylactic shock. Alexander and Bottom repeated these experiments. They found that treatment of guinea pigs with histaminase fifteen minutes before injection with histamine failed to protect against histamine shock. Similarly, histaminase did not protect against anaphylactic shock. The histaminase used in these experiments was found to be potent and devoid of toxic effects.

Studies on In-Vitro Anaphylaxis and Release of an Active Non-Histamine Material From Sensitized Guinea Pig Lung. Campbell, D. H., and Nicoll, P. A.: J. Immunol. **39**: 103, 1940.

The present investigations were carried out to ascertain whether the substance released from sensitized guinea pig tissue would induce contraction of normal rat uteri, which are relatively refractory to histamine. It was determined that 20 gamma per milliliter or more of histamine was required to produce contraction of uterine muscle of the rat.

Normal rat uteri, suspended in the Dale bath which also contained sensitized guinea pig lung tissue, responded with marked contraction to the addition of specific antigen to the bath. Rat uteri remained unaffected by preliminary testing with ordinary doses of histamine but responded with strong contractions to addition of acetylcholine to the bath even after previous specific contraction. The authors believe that some substance, other than histamine, is released by sensitized guinea pig lung tissue following its interaction with specific antigen. The response of normal rat uteri to the substance released by guinea pig lung was usually greater than that obtained by the addition of specific antigen directly to sensitized rat uteri.

Uterine muscles from sensitized pregnant guinea pigs were found to be at least as good for anaphylactic studies as those from virgin guinea pigs. Intestinal strips obtained from 7- to 8-week-old guinea pig fetuses removed from sensitized mothers showed specific contractions in the Dale bath.

The Liberation of a Slow-Reacting Smooth Muscle-Stimulating Substance in Anaphylaxis. Kellaway, C. H., and Trethewie, E. R.: Quart. J. Exper. Physiol. **30**: 121, 1940.

In the Dale bath, the response of the isolated jejunum from sensitized guinea pigs to the addition of the specific anaphylactic antigen resembles that produced by venoms and by S. R. S. (slow-reacting smooth muscle-stimulating substance). The similarity is apparent in respect to latent periods, the time required for relaxation of the muscle strip, and the after-changes in excitability of the muscle. The slow-reacting smooth muscle-stimulating substance may be prepared from tissue constituents by enzymic actions of venoms.

In addition to histamine, a substance with an action similar to S. R. S. appears in the perfusate from sensitized lungs after the arterial injection of specific antigen.

The authors conclude that the anaphylactic contraction of smooth muscles is in part due to the liberation of histamine and probably in part also to S. R. S., which is liberated from the tissues and not formed in the antigen-antibody reaction.

Quantitative Investigation of the Changes in Antigenic Properties in the Course of Iodination of Horse-Serum Globulin. Kleczkowski, A.: Brit. J. Exper. Path. **21**: 98, 1940.

In the course of iodination of horse-serum globulin, the ability to react with and the ability to produce antibodies to native globulin disappear simultaneously

when the Folin color value of the newly formed compounds falls to about 30 per cent of the original value. There is suggestive evidence that this loss of species specificity occurs when all the tyrosine is substituted. When the Folin color value falls only to 40 per cent, the iodized globulin reacts strongly with antisera to native globulin and in the excess antigen zone forms even more precipitate than does the native globulin. This is attributed to changes in the physical properties of the globulin molecule induced by the treatment.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Concerning Eczema-Death. Koch, H.: Arch. f. Kinderh. **119**: 209, 1940.

The sudden death of infants with eczema was at first looked upon as being due to *status lymphaticus*. Paltauf described the latter condition and considered it a sign of constitutional inferiority. Where sudden death occurred, he ascribed it to damage to the nerve tissue of the cardiac regulating centers.

An instance of sudden eczema-death is reported in which myocardial damage was found at post-mortem examination. Diphtheria bacilli were also cultured post mortem from areas of necrosis behind the ears, which did not resemble diphtheria clinically. Others have reported sudden death in cases of atypical skin diphtheria.

The question is raised whether instances of sudden eczema-death may not be due to unrecognized skin diphtheria in patients whose skin response to such an infection is decidedly atypical and therefore unrecognized.

A Simple Specific Precipitation Test for Cow's Milk. Gnosspelius, A.: Arch. Dis. Child. **15**: 171, 1940.

In conducting a breast milk station, the need for a simple method of detecting the addition of cow's milk to breast milk arose. Several colorimetric methods previously described were found inadequate. The anaphylactic test was not practical, and the complement fixation test was too cumbersome.

A modification of the usual precipitation reaction, which was highly successful, was developed. It consisted in mixing on a slide a few loopfuls of sensitized rabbit serum with a few loopfuls of the fat-free milk to be examined. Within a few minutes microscopic and even macroscopic flocculation occurs if there is 1 per cent or more of cow's milk present. The mother's diet does not affect the test.

To obtain a titer of 1:20,000 or more in the rabbit serum, Gnosspelius injected 5 c.c. of milk intravenously on alternate days for five injections. The last injection was given with great care to avoid anaphylactic shock. On the fourth day after the last injection the rabbit was bled.

Treatment of Infantile Eczema. Ward, C. E.: Mississippi Doctor **18**: 451, 1941.

Seborrheic dermatitis, most often seen in fat, breast-fed babies, responds well to a low fat diet and 1 per cent salicylic or 1 per cent sulphur ointments. Contact dermatitis is best illustrated by rhus sensitivity. Atopic eczema is more common than either seborrhea or contact dermatitis and is more difficult to treat. Milk is the most common offender, and environmental allergens have to be considered at all times. The diet of the mother of a breast-fed baby may have to be altered, or the baby weaned. Feathers, animals, and woolen clothing and blankets are eliminated from the sphere of the child's activity.

Boric ointment, 3 per cent ichthyol in zinc oxide ointment, and tar ointment are the most useful local applications. It may be necessary to use a wet dressing of

boric solution or 0.5 per cent aluminum subacetate solution first, if there is much oozing or secondary infection. The success of treatment depends largely on the degree of cooperation obtained in carrying out directions. Skin tests are of little practical value in small infants.

Suprarenal Gland and Lactose in the Treatment of Major Allergic Disorders in Childhood. Lockey, S. D.: Arch. Pediat. **57:** 724, 1940.

Whole suprarenal gland concentrate and lactose were given by mouth to a group of 163 children with the complaint of asthma, eczema, or hay fever. It is the author's impression that all three disorders were lessened by this treatment. Duration of treatment and dosage varied.

Control groups did uniformly less well. In some instances, cessation of medication was followed by a return of symptoms, which were again completely relieved on resumption of medication. Environmental control, desensitization, dietary manipulation, and medication were used as seemed indicated in both the controls and those receiving the gland preparation and lactose. Details of dosage and symptoms are mentioned in six cases.

Asthma Complicated by Subcutaneous Emphysema in Children. Skinner, H. H.: J. Pediat. **18:** 117, 1941.

Seven instances of subcutaneous emphysema accompanying asthma in children have been reported previously by various authors, and this report adds one more. The patient was an 8-year-old girl who had had attacks of asthma over a period of three years or more. She had also had a severe attack of pertussis at the age of 3 years.

During the course of an asthmatic attack, subcutaneous emphysema appeared over the left scapula, left axilla, the upper chest, and the neck. It persisted for ten days and then completely disappeared.

The author believes that the fascial reflections are such that it is not likely that the air comes from the apices of the lungs or follows the large vascular trunks. It probably comes through an area where the parietal and visceral pleura are adherent and enters the mediastinum without establishing a pneumothorax.

Eczema of Infancy and Early Childhood: Its Pediatric Management. Bost, C.: California & West. Med. **54:** 24, 1941.

Eczema at this age is most often atopic dermatitis; but seborrheic dermatitis, contact dermatitis, and occasionally a fungus dermatitis also occur and are referred to as eczema. The pediatrician is in an advantageous position for studying and treating these conditions, since he usually has followed the patient since birth and observed the dermatitis at all stages.

Seborrheic dermatitis does not itch and responds to reduction or alteration of fat in the formula. Atopic dermatitis itches severely, and local treatment with ointments and restraints is directed largely at this symptom. Meanwhile, diet manipulation and environmental control, aided by visits to the home, help in bringing the eczema under better control. Skin tests, while not necessary in all cases, are useful in narrowing down the number of substances in the environment on which the greatest emphasis should be placed.

Eczema in older children presents a much more difficult problem than it does in the younger group. The difficulty of their care makes it apparent that at present our understanding of the problem is rather meager.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Allergic Conjunctivitis. Bowen, R.: South. M. J. **34**: 184, 1941.

In discussing the matter of allergic conjunctivitis, Bowen classifies this disease into two types, the vernal and the nonvernal. He believes that vernal conjunctivitis is a form of contact dermatitis and that its treatment is expedited by using both the water and the fat soluble antigens. He feels that the nonvernal type may be the result of cosmetics, drugs, bacteria, foods, environment, pollen, and fungi. Close cooperation between the ophthalmologist and the allergist is recommended. In the practical management of these cases it is suggested that the physician personally visit the patient's home and place of employment.

The Treatment of Chronic Obstructive Rhinitis With Submucosal Injections of Sodium Psylliate. Thacker, E. A.: Ann. Otol., Rhin. & Laryng. **49**: 939, 1940.

Thacker reports his results in the treatment of chronic obstructive rhinitis with submucosal injections of sodium psylliate. One-fourth to 0.5 c.c. of 5 per cent sodium psylliate is injected into the inferior turbinate, on one side at a sitting. He states that in chronic rhinitis in which the mucosa fails to shrink well with cocaine, adrenalin, or ephedrine treatment with sclerosing agents is not indicated. This method of treatment is recommended in the treatment of nasal allergy which has not responded to allergic management. He reports the complete relief or improvement of nasal obstruction in twenty-four patients treated by this method. The number of injections necessary to produce the desired effect ranged from one to four in the same turbinate, with an average of two injections being sufficient in the majority of instances.

Intranasal Vaccine Spray: Its Use in Prophylaxis Against the Common Cold. Walsh, T. E.: Ann. Otol., Rhin., & Laryng. **49**: 875, 1940.

Walsh reports his extensive observations on the use of intranasal vaccine spray as prophylaxis against the common cold. He points out that the prophylaxis of colds by the use of subcutaneous injections of vaccines has proved to be disappointing. He presents experimental evidence to show that the rational method of vaccination against the common cold is by the local application of vaccines to the nasal mucosa. The results are tabulated in the treatment of 384 patients over a period of eight years. Of a total of 627 patient-years of vaccination, there were 74 per cent good results, 10 per cent fair results, and 16 per cent failures. Control experiments were conducted on 144 patients. It is finally suggested that the results warrant the conclusion that the method of local vaccination against the common cold offers the best method of prophylaxis at our disposal.

The Course of Inspired Air and the Possibility of Aspiration of Mucopus From One Side of the Nose Into the Corresponding Lung. Van Dishoeck, H. A. E.: Acta Otolaryng. **27**: 414, 1939.

In a series of experiments on the aspiration of coal dust, van Dishoeck noted that the mixing of air inspired through both nostrils is perfect before it reaches the trachea, granted that both sides of the nose are of equal caliber. When, however, one side of the nose is narrow and the other is wide, the weak current of the narrow side will be carried along laterally in the strong current of the wide side and will not mix well. In such a case, the current will sweep air from the narrow side of the nose to the lung of the same side and not into the other

lung. The author does not believe that the same thing takes place when mucopus is under consideration in cases of one-sided sinal infection, because the air current from the stenosed side of the nose is too weak to carry along the sticky mucopus. This can also be shown by having a patient with a one-sided sinal infection forcibly exhale from that side of the nose through a tube having the same pattern as the nose, pharynx and trachea. If a glass slide is held at the end of the tube it is noted that on normal and forced expiration droplets are not carried off with the air stream. From these experiments, van Dishoeck concluded that pulmonary infection by means of aspiratory drops in cases of nasal infection is of little consequence, and that the chance of infection of the lung on the same side is slight.

Angioneurotic Edema of the Larynx Due to Sensitivity to Chicle. Frank, D. I.: Arch. Otolaryng. **32**: 1067, 1940.

Frank reports a very interesting case of angioneurotic edema of the larynx due to sensitivity to chicle. He calls attention to the fact that in differentiating the angioneurotic from other types of laryngeal edema, the former or the allergic edema is usually associated with other manifestations of allergy, such as urticaria or angioneurotic edema of the skin, nasal allergy, or gastrointestinal allergy. In examination of the larynx he states that angioneurotic edema does not appear as if a puncture would liberate water. It appears firmer in consistency. He calls attention to the report of Jackson, who pointed out that 33 per cent of the patients who have died from angioneurotic edema of the larynx had a fatal termination because of the want of prompt tracheotomy. The case reported by Frank was a man, aged 22 years, who, five minutes after the ingestion of chewing gum, noted a lumpy choking feeling in his throat together with a sensation of dryness and nausea which prompted him to expel the gum immediately. Soon afterwards his face and extremities began to swell, and he felt itchy. There was a watery discharge from the nose associated with sneezing. Within an hour he developed nausea and vomiting. Examination of the patient showed a generalized giant urticaria, suffusion of the conjunctiva with lacrimation, coryza, syncope, and vomiting. A nasal examination showed a typical allergic membrane. The larynx presented a moderate to marked edema of both arytenoids and aryepiglottic folds as well as slight edema of the epiglottis. The glottic space was definitely narrowed, but not sufficiently to cause any dyspnea. Following the injection of 10 minims of adrenalin, the patient began to show improvement. Within two hours after the onset of the attack, the larynx was entirely normal. In three and one-half hours after the onset there was little remaining evidence of the generalized edema and giant urticaria. Intracutaneous tests showed marked reactions to several inhalants and foods. Intracutaneous tests using an extract of chicle showed very pronounced reactions. Serum was obtained from the patient for passive transfer and was administered to five normal subjects. One of the subjects gave a definite positive reaction to the transfer test on the area of skin sensitized to the solution containing 0.015 mg. per cubic centimeter.

Bronchial Collapse Without Clinical Signs of External Pressure: Bronchoscopic Observations. Bozer, H. E.: Ann. Otol., Rhin., & Laryng. **49**: 1091, 1941.

Bozer states that the bronchoscopic observation of the collapse of a main bronchus without any evidence of external pressure is apparently very uncommon, since he has failed to find a report of such observations during the last twenty years. He reports in detail the observations made in three patients. Dyspnea was one of the outstanding symptoms. One of the patients had asthma. In two of the patients the obstruction of the main bronchus was complete. Diagnosis was established by brochoscopic vision so the nature of the obstruction was unquestionable. It is suggested that the

reason for the collapse was either the occurrence of an exceedingly strong spasm of the bronchial musculature or the presence of structural weakness in the walls of the bronchus.

The Use of Colloidal Thorium Dioxide in Roentgenography of the Paranasal Sinuses. Grove, R. C.: Laryngoscope **50:** 1165, 1940.

In using iodized oil as an opaque medium in x-ray examinations of the sinuses, Grove states that, because of the density of the shadows produced, small polypoid changes or membranous thickening are often not visible in certain portions of the antra. He therefore suggests the use of colloidal thorium dioxide solution, which is also designated as "Umbrathor." Umbrathor is a colloidal solution containing 25 per cent thorium dioxide. Following its use in seventy-five allergic cases, there has been no untoward reaction. Its use has been more satisfactory than iodized oil because no instances of sensitivity were observed. Because it is in aqueous form, it may be injected easily in diluted strengths and is, therefore, inexpensive. It gives a clear, delicate delineation of slight polypoid changes which are often obscured by iodized oil. It is nonirritating and nontoxic. Grove states that in seventy-five antra injected with this solution the findings were confirmed in 30 per cent of the cases by the Caldwell-Luc operation.